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(54) **USE OF COMPLEXES FOR THE PREPARATION OF COMPOSITIONS FOR THE TREATMENT OF SENSITIVE SKIN, PREPARATION PROCESS AND HYPOALLERGENIC COMPOSITIONS**

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Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(58) **Field of Search** 424/401, 520, 424/195.1; 514/2, 23, 458, 844, 937

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(57) **ABSTRACT**

The present invention relates to the use of at least two compounds chosen from components having an a) anti-radical, b) anti-inflammatory and c) anti-allergic activity for the preparation of a composition exhibiting at least two of the a), b) and c) activities intended for the treatment of sensitive and/or allergic skin. It also relates to a process for the preparation of such compositions and to the compositions thus obtained.

9 Claims, 2 Drawing Sheets

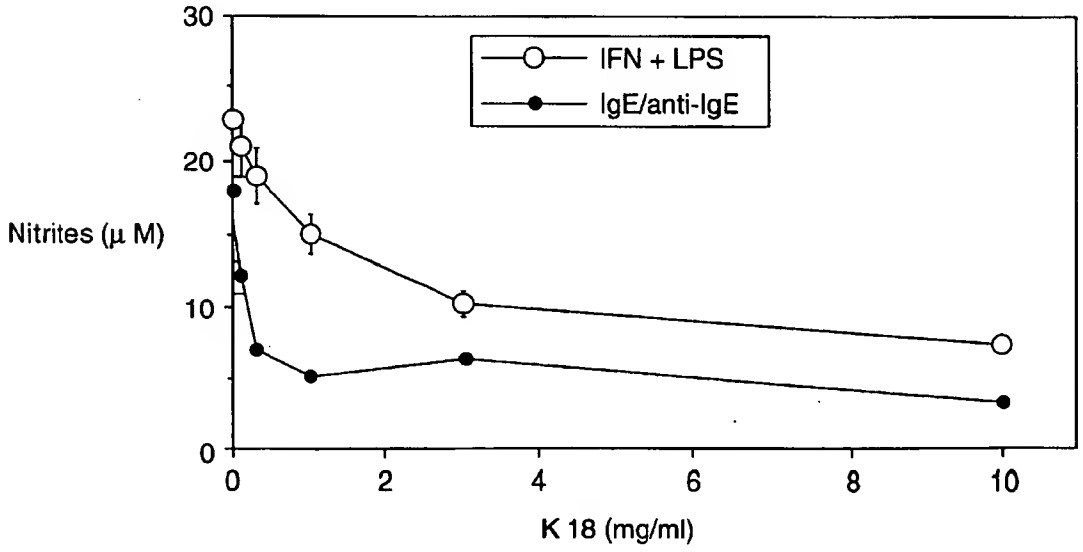


FIG. 1

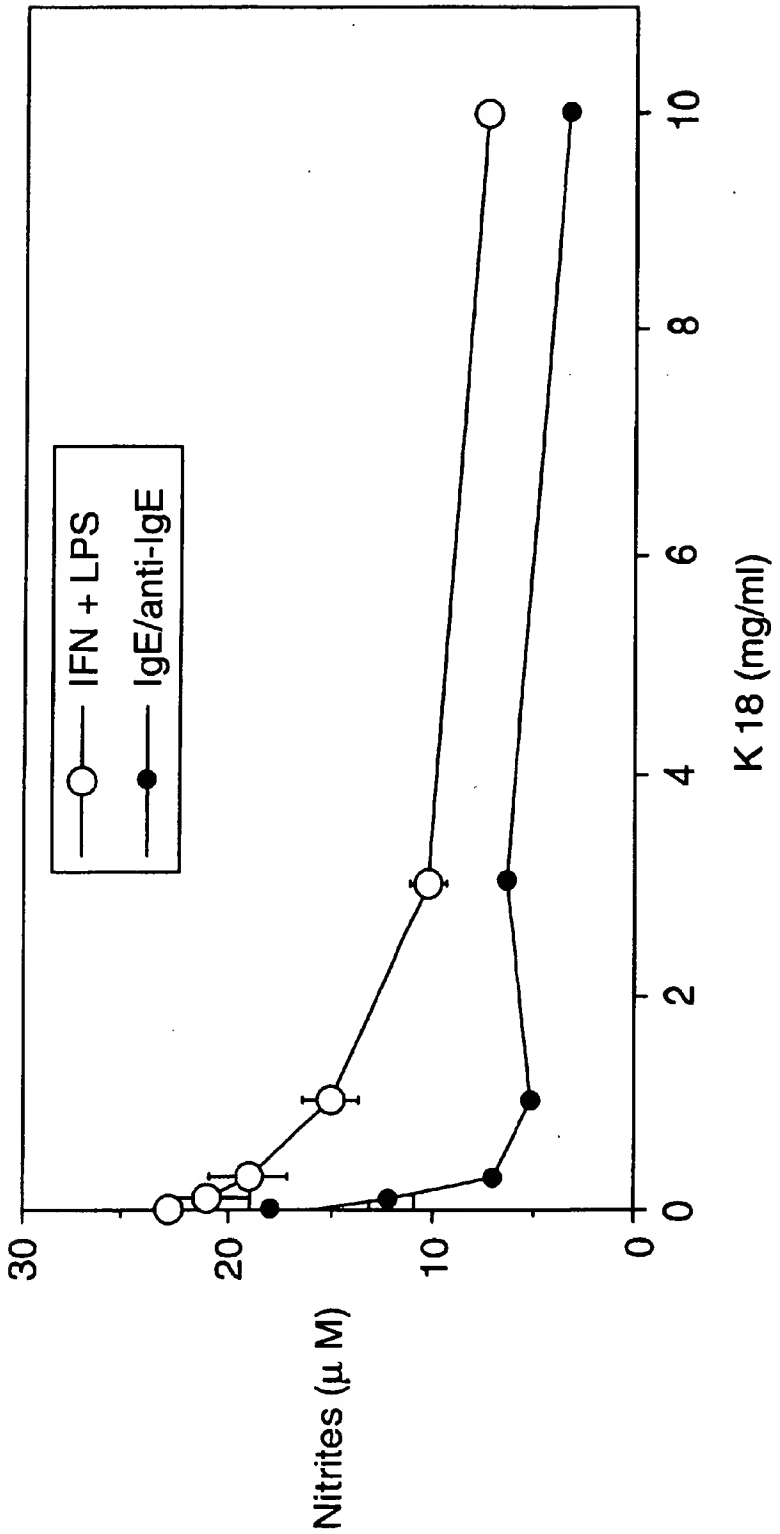
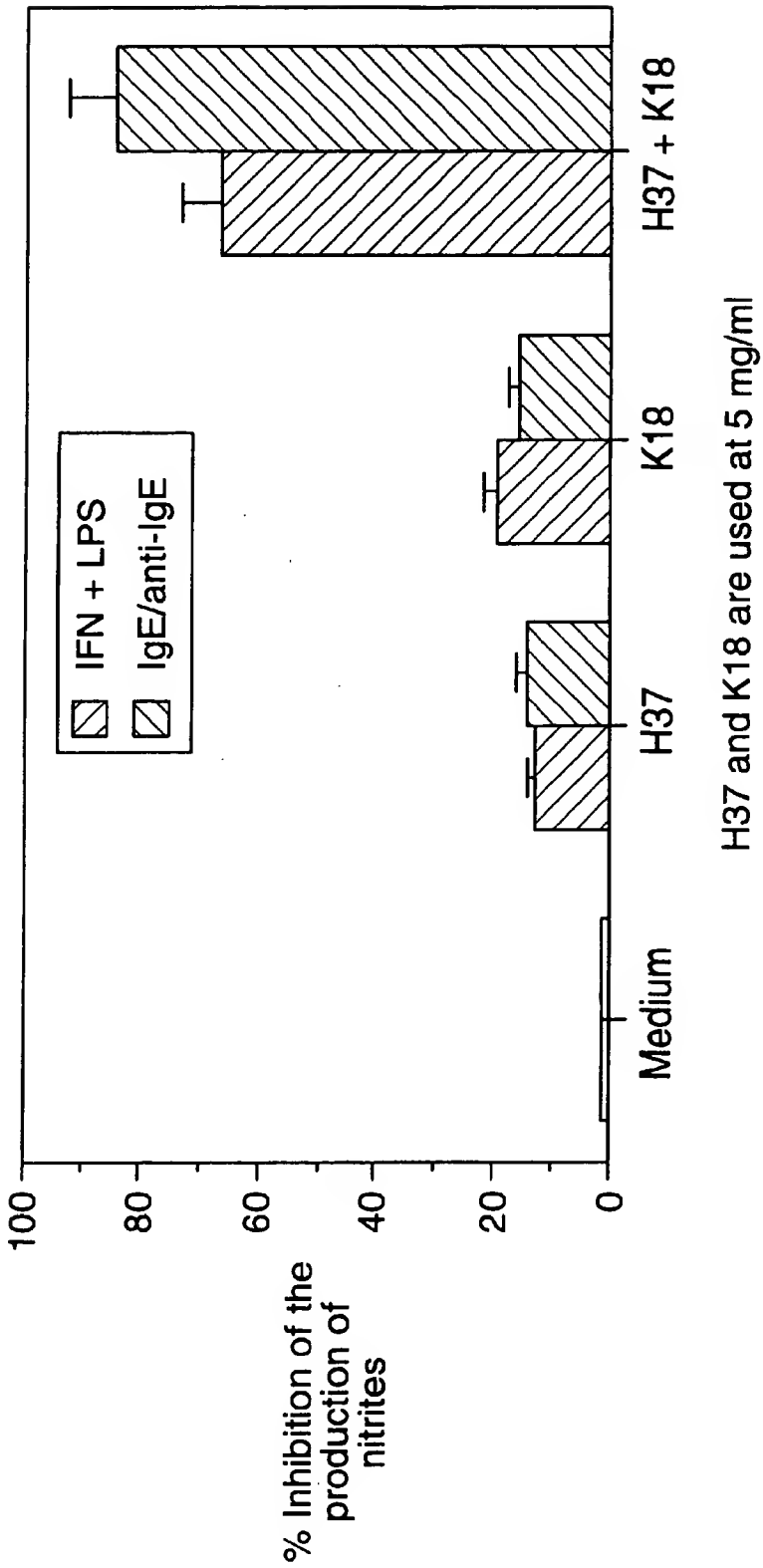


FIG. 2


IFN + LPS
IgE/anti-IgE
100
80
60
40
20
0
% Inhibition of the production of nitrites
Medium
H37
K18
H37 + K18
H37 and K18 are used at 5 mg/ml

USE OF COMPLEXES FOR THE PREPARATION OF COMPOSITIONS FOR THE TREATMENT OF SENSITIVE SKIN, PREPARATION PROCESS AND HYPOALLERGENIC COMPOSITIONS

The invention relates to new dermocosmetic and pharmaceutical compositions which are useful for improving and treating hyperreactive skin conditions and more generally allergic-type reactions and/or intolerance phenomena, whether they are caused by external factors or factors intrinsic to the individual.

Increasing numbers of children and adults are in fact exhibiting skin described as "sensitive". During a recent study in France, 70% of the women questioned stated that they had sensitive facial skin. The notion of sensitive skin covers an array of outward signs comprising reactive skin and intolerant skin. Atopic skin can also be included therein. These skin types are sometimes incorrectly known as "allergic" by the subjects; however, while an allergic component can sometimes be evoked in the symptoms of sensitive skin, it may not be restricted to it. The triggering factors can be environmental attacks such as wind, pollution, temperature variations, excessively hard water or ill-suited hygiene, cosmetic or care products; these phenomena can also be associated with stress or emotions felt by the subject, some diets or the taking of medicaments. In addition, there exists individual predisposing factors (in particular neurological or hormonal) or familial predisposing factors which amplify these reactions.

Generally, the subject feels cutaneous discomfort which can manifest itself by subjective and/or objective signs. The skin readily gives off stabbing pains, itches or smarts and the subject may experience feelings of warmth, pricking or burning on the skin. The skin can redden or desquamate. Xerosis, seborrhoeic dermatitis, telangiectasias, vesicles or even oedema is observed, on an irregular basis.

In the most serious cases, dermatological complaints of immunoallergic type, such as atopy, eczema or neurodermatitides, may be observed.

This condition can manifest itself on the skin, the mucous membranes or the scalp. In the latter case, it may be associated with a dandruff condition and/or alopecia.

Until now, attempts have been made to prevent the appearance of these reactions by limiting the presence, in dermocosmetological formulations, of components known to be allergizing. However, it would be desirable to be able to have available truly active compositions which are capable of preventing or of relieving these symptoms by decreasing the reactivity of the skin and by improving its resistance to the triggering factors.

The Applicant Company has now found, unexpectedly, that these aims could be achieved by the use of a composition containing a synergic combination producing an active hypoallergenic complex.

Such a complex will, in addition, improve the receptivity of the skin towards other active principles.

For this reason, the subject of the present invention is a dermocosmetic composition, characterized in that it contains an immunomodulatory or hypoallergenic synergic combination of at least two components, each of these components exhibiting at least one of the following activities:

a) anti-radical

b) anti-inflammatory

c) anti-allergic,

the said components being chosen so that at least two activities a), b) or c) are present in the composition.

The subject of the invention is more particularly the use of at least two compounds chosen from components having an a) anti-radical, b) anti-inflammatory and c) anti-allergic activity for the preparation of a composition, in particular an immunomodulatory composition, exhibiting at least two of the a), b) and c) activities intended for the treatment of sensitive and/or allergic skin; according to one of its aspects, the a), b) and c) activities are exerted in the composition.

Indeed, the Applicant Company has been able to show that the combination of active principles having complementary anti-allergic, anti-radical and/or anti-inflammatory activities made it possible to effectively combat the phenomena associated with the appearance of the symptoms of sensitive and/or intolerant skin or of immunoallergic complaints, preferably via a synergy of the activities of the components.

The components forming part of the formulations according to the invention can be purified or unpurified molecules, synthetic or extracted products, mixtures of active principles or extracts which have been subjected to one or a number of fractionation stages from a starting material of plant or animal origin.

Preferably, if two components present in the formulation show an activity of the same type, it will be exerted by the involvement of a different mechanism.

As regards the anti-inflammatory activity, it can in particular be provided by prostaglandin inhibitors (cyclooxygenase route), inhibitors of cytokine production and inhibitors of the production of leukotrienes (LTB, for example, lipoxygenase route).

The component or components with anti-inflammatory activity advantageously exhibit an inhibiting activity on the production of IL-1, IL-2, IL-4, IL-5, IL-12 and/or TNF-α (Tumour Necrosis Factor).

The anti-inflammatory function can also have the consequence of decreasing the production of reactive nitro derivatives by the cells, limiting the generation of free radicals.

However, anti-radical activity is understood to mean components which are preferably chosen from free-radical scavengers, anti-lipoperoxidants and stimulants of the endogenous production of the enzymes which degrade free radicals.

Free radicals, by definition, are neutral or charged chemical species which have an unpaired electron. This "single electron" endows them with specific chemical properties and a short lifetime. They are reaction intermediates which will be stabilized by combination or transfer and can be the source of a chain reaction. Mention may be made, among free radicals, of the superoxide anion $O_2$the hydroxyl radical OH , NO or peroxides.

Enzymes which are active in endogenous defense systems against free radicals are, for example, SOD (or superoxide dismutase), catalase or glutathione peroxidase; attempts will be made to stimulate the production of these enzymes or they can be introduced exogenously.

The components providing the anti-allergic function in the composition according to the invention are preferably chosen from inhibitors of lymphocyte proliferation, inhibitors of the internalization of the molecules of the major histocompatibility complex (HLA-DR, for example) or inhibitors of cytokine production. They are advantageously capable of decreasing the production of the mediators of the inflammation which occurs during allergic phenomena.

As indicated above, the composition will exhibit at least two of the anti-radical, anti-inflammatory and anti-allergic activities. In addition, the components of the active hypoallergenic complex will be chosen so that a synergy is exerted via different mechanisms at the basis of the same activity.

Each component will preferably contribute, via a number of parameters, to the overall activity of the composition according to the invention.

The composition according to the invention advantageously has a marked inhibiting activity on the synthesis

and/or the expression of neuromediators, in particular with respect to cutaneous cells, resulting from a synergy of the activities of its different components. The neuromediators can be chosen from the group comprising neurokinines A (NKA) and B (NKB), vasoactive intestinal polypeptide (VIP), calcitonin gene related peptide (CGRP), neuropeptide Y (NPY), neurotensin (NT), somatostatin (SOM), gastrin releasing peptide (GRP), nerve growth factor (NGF), PGP 9.5 (Protein Gene Product 9.5) and bombesin.

Components making possible the preparation of dermocosmetic compositions according to the invention can advantageously be chosen from the following group: Ginkgo biloba and its extracts, iramine, D-panthenol, β-sitosterol, modulene, α-tocopherol and its derivatives, β-glucan and its derivatives, eicosapentanoic acid, 18β-glycyrrhetinic acid, glycyrrhetinic acid monoglucuronide, stearyl glycyrrhetinate, Scutellaria extract, lactoferrin, green tea and its extracts, vitamin C, glutathione, epidermal thymus factor, azole derivatives and lipacid.

However, the combination of vitamin E with a Scutellaria extract is not included within the compositions according to the invention.

According to one of the aspects of the invention, the composition contains at least one component, preferably at least two components, chosen from the above group.

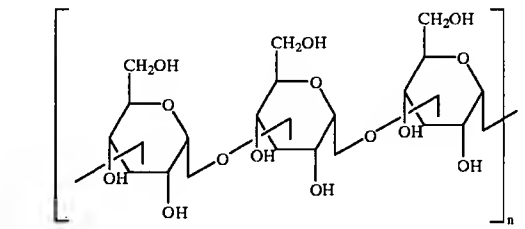
The azole derivatives used according to the invention can be chosen from imidazole or triazole derivatives and in particular from the group composed of: bifonazole, butoconazole, chlordantoin, chlormidazole, cloconazole, clotrimazole, econazole, enilconazole, fenticonazole, flutrimazole, isoconazole, ketoconazole, lanoconazole, miconazole, omoconazole, oxiconazole, sertaconazole, sulconazole, tioconazole, fluconazole, itraconazole, saperconazole, terconazole or elubiol.

This is because it has now been possible to demonstrate that these compounds exhibit in particular an anti-radical activity.

Mention may more particularly be made, among α-tocopherol derivatives which can be used, of α-tocopherol phosphate.

Mention may be made, among β-glucan derivatives, of carboxymethyl-β-glucan and drieline.

Drieline is a poly-β(1→3)-glucopyranose of formula



n = 1000

with n=1000.

The molecule can be provided in the form of a 0.1% solution in water and sorbitol or in the powder form.

In one of the preferred embodiments of the invention, the composition contains a synergic combination of a Ginkgo biloba extract and of a β-glucan compound.

Indeed, the Applicant Company has found that the combination of these two components made it possible to obtain the optimum combination of the functional characteristics providing the activity of the compositions according to the invention.

The glucan is composed of a β(1→3) glucose chain which can in particular be extracted from the wall of yeast cells. It is possible to subject it to chemical modifications in order in particular to improve its solubility.

The β-glucan is advantageously substituted by carboxymethyl groups; it can exist in the salt form, in particular the sodium salt form. Good results are obtained with a derivative in wich the degree of substitution by carboxymethyl groups is within the range from 0.65 to 0.85 and which exhibits a pH from 5.5 to 8.5.

Ginkgo biloba is a dioecious tree from the Far East, the leaves of which are used for certain medicinal properties. They contain constituents, such as aliphatic hydrocarbons and alcohols, polyphenols, such as luteolin or quercetol, or biflavones derived from amentaflavone, and more specific constituents: ginkgolic acid, and anacardic derivatives, terpenes derived from limonene or terpenes containing a tert-butyl group.

Ginkgo extracts have been proposed for improving the symptoms of mental deficiency in the elderly, of intermittent claudication, of obliterating chronic arteriopathies and of Raynaud's disease, or in the case of retinal deficiency.

They have been used in cosmetology for their protective effect with respect to free radicals.

The Applicant Company has found, unexpectedly, that ginkgo extracts have an excellent anti-inflammatory and anti-allergic activity which can be demonstrated on cutaneous cells, such as keratinocytes and macrophages. In addition, the Applicant Company has shown that this activity is potentiated in the presence of β-glucan.

Extracts which are particularly suitable for the implementation of the invention are obtained from Ginkgo biloba leaves which have been subjected to a stage during which the terpene concentration has been brought to a value of less than approximately 7% and preferably of less than approximately 3% (w/w of dry extract). In one of the embodiments, this terpene concentration is less than approximately 1% w/w.

The concentration of flavone heterosides in the dry extract is advantageously greater than 24% and preferably greater than approximately 28% w/w.

The anti-inflammatory and anti-allergic properties can be demonstrated in particular with respect to in vitro models, for which a correlation exists with animal models and clinical studies already carried out on man.

It is possible in particular to operate on keratinocytes and macrophage cells because these are cells which are essential for the development of a local inflammatory reaction. Moreover, macrophages are particularly advantageous cells because, due to the fact that these are resident cells in the skin, they regulate not only local inflammatory reactions but they also regulate the immune responses by their ability to present the antigen and to produce a great number of cytokines which regulate local immunity. These macrophages are also involved in communications with the circulatory system which can, if appropriate, mobilize different cell types (monocytes, neutrophils, eosinophils and T lymphocytes), thus increasing the non-specific and specific defensive power of the tissue under consideration.

The activities of the test products are therefore investigated with respect to human macrophage and keratinocyte cultures which are or are not stimulated by interferon-γ+ lipopolysaccharide (non-specific inflammation) or by IL-4 (allergic inflammation). This type of stimulation places the cells in the context of a pro-oxidizing response (generation of NO or superoxide anion free radicals, which can be evaluated by measuring the production of nitrogenous derivatives) and an immuno-inflammatory response (production of cytokines such as TNF-α).

To evaluate the allergic inflammation, the cells are activated by IL-4, which induces the CD23 receptor, and then by IgE-containing immune complexes. In all cases, the cellular supernatants are analysed after the activation.

A viahility study is in addition carried out on the cells.

The activity of the components is also confirmed on mixed lympho-cpidermal cultures (MLEC).

In the skin, Langherans cells indeed play an essential role in the presence of the antigen and keratinocytes generate factors which are involved in the immune responsc, thus constituting a cutaneous immune system. MLECs make it possible to determine the immuno-modulatory properties of substances hy measuring thc lymphocyte proliferation induced hy the antigen-presenting allogenic epidermal cells, with or without treatmcnt by thc suhstance.

The results obtained with ginko and β-glucan are summarized in the table below:

Activity	Mediator or parameter	Ginkgo biloba	β-Glucan
Anti-inflammatory	LTB_4	inhibition	no effect
	PGE_2	no effect	inbibition
	IL-1α	no effect	inhibition
	TNF-α	no effect	inbibition
Anti-free radicals	peroxidation of the lipids	inhibition	no effect
	NO	inhibition	inhibition
	catalase	no effect	stimulation
	glutathione peroxidase	stimulation	stimulation
Anti-allergic	MLEC	inhibition	no effect

Compositions according to the invention contain in particular from 0.001% to 10% w/w of a ginko extract and preferably from 0.05 to 2%; according to one of the emhodiments, the concentration of ginkgo extract will he from approximately 0.1 to 0.5% hut it will he adjusted by the person skilled in the art.

Concentrations of β-glucan, in particular carhoxymethylated β-glucan, which are suitable for the implementation of the invention are within the range from 0.001% to 10% w/total w of the composition.

Other compositions which are particularly suitable for the invention comprise the combination of lactoferrin and drieline, panthenol and green tea extract or panthenol and β-sitosterol. A combination of β-tocopherol (or one of its salts) and a ginkgo extract can also he used according to the invention. Such combinations produce an active hypoallergenic complex which lowers the reactivity threshold of the skin and of the scalp and decreases the magnitude of the possible intolerance or immunoallergic reactions.

The green tea extract is obtained from dry Camellia oleifera leaves and contains, in particular, theophylline, caffeine and theobromine.

Another subject of the invention is a process for the preparation of an active hypoallergenic complex, characterized in that substances belonging to at least one of the groups: anti-free radical, anti-inflammatory and immunomodulatory active principle are selected and in that two substances having complementary activities are then comhined so as to potentiate the anti-radical, anti-inflammatory and anti-allergic functions of the comhination.

The comhination of the substances constituting the active hypoallergenic complex preferahly decreases the synthesis or the expression of the neuromediators, such as VIP, PGP 9.5 or CGRP, which are correlated with so-called "sensitive" or irritable skin.

Another subject of the invention is a method for the cosmetic treatment of sensitive skin comprising the application to the skin of the body or of the face, one or a number of times per day, of active hypoallergenic complexes and/or compositions as defined above.

In particular, the invention relates to a method for the treatment of alopecia which comprises the weekly, twice-weekly, daily or twice-daily application to the scalp of a combination of anti-radical, anti-inflammatory and/or anti-allergic components. The comhinations can be in different formulations, such.as shampoos or lotions, which can he applied simultaneously, separately or sequentially, optionally with other active principles which are active with respect to alopccia, dandruff conditions and/or seborrhoeic conditions.

Another of the subjects of the invention is the use of a hypoallergenic complex as defined above for the preparation of an immunomodulatory medicament, in particular intended for the treatment of a complaint chosen from atopy, psoriasis, erythema multiforme, xeroder-maztitides, lupus erythematosus, pemphigus, dermatitides, rosacea, acne, eczemas and neurodermatitides.

The hypoallergenic comhinations according to the invention will advantageously he formulated within compositions also containing moisturizing agents and/or agents which improve cutaneous penetration, which will promote the activity of the complex according to the invention. Mention may he made, hy way of examples, of urea, propylene glycol or oleic acid, the person skilled in the art heing capahle of using other penetration promoters suited to the type of formulation.

The compositions according to the invention will in addition contain pharmaceutically and/or cosmetologically accceptahlc excipicnts known to the person skilled in the art suited to their formulation, in particular in the form of solutions, lotions, creams, shampoos, emulsions, and the like.

Mention may he made, in a non-limiting way, of pigments, dyes, preservatives, texturing agents, thickeners, emulsifiers or fragrances. They can also contain sunscreening agents or blockers or another active principle.

Finally, the hypoallergenic complexes containing the combinations according to the invention can be introduced into compositions containing at least one active principle hy the topical route, in particular when this active principle is capahle of causing a cutaneous reaction.

Mention may more particularly be made, among such active principles, of retinoids and depigmenting active agents.

Retinoids is understood to mean in particular retinoic acid or tretinoin, retinol, retinaldehydes, their salts and their esters. The alkali metal, ammonium and C_2–C_{30} ammonium salts are typical salts. The sodium, potassium, triethanolammonium and ammonium salts are particularly preferred. The comhinations of all the ahove compounds can he present in thc compositions. In addition, the terms "retinol" and "retinoic acid" must he understood as including the hydrogenatcd and non-hydrogenated isomcrs, such as 9-cis-retinol, didchydro-retinol, 13-cis-rctinoic acid, 13-trans-retinoic acid and didehydroretinoic acid.

The depigmenting agents comprise, for example, kojic acid, hydroquinone, vitamin C, vitamin C magnesium phosphate, carotenoids, arbutin, and the like.

The following examples are intended to illustrate the invention.

In these examples, reference will be made to the following figures:

FIG. 1: Dose effcct of carhoxymethyl-β-glucan with respect to thc inflammatory functions of the keratinocytcs.

FIG. 2: Synergy between a Ginkgo biloba extract (H37) and carboxymethyl-β-glucan (K18) in their anti-inflammatory functions with respect to keratin-ocytes.

EXAMPLE 1

1. Materials and Methods

Products

The following products were used during this study: *Escherichia coli* LPS (Sigma), used at 1 μg/ml. IFN-γ and IL-4 are sourced from Immugenex (Los Angeles Calif.) and are used respectively at 1000 U/ml and 10 ng/ml, the monoclonal IgEs are sourced from Stallergène (Fresnes, France) and the anti-IgEs are from Nordic (Tilburg, Holland).

Keratinocyte culture

The keratinocyte primary cultures are obtained from neonatal foreskins and are maintained in proliferation ex vivo in a medium which does not contain calf serum. The confluent keratinocyte cultures are trypsinized and transferred into 24-well plates in fresh medium at the cellular density of 10^5 cells/ml/well. If appropriate, in the case of stimulation by IL-4, the presence of the IgE receptor (CD23) at the surface of the cells is verified by immunolabelling.

Macrophage culture

The macrophage cells are obtained from the peripheral blood of normal donors (non-allergic). The mononuclear cells are isolated on a ficoll gradient and the ring of lymphoid cells is recovered and washed three times and the cells are then cultured so as to cause the macrophage cells to adhere. These cells are recovered after adhering for 1 hour and are cultured (10^6 cells/ml/well). If appropriate, in the case of stimulation by IL-4, the presence of the IgE receptor (CD23) at the surface of the cells is verified by immunolabelling.

Cell activation

The cells are activated by the combination of IFN-γ and LPS for 3 to 4 days and the supernatants of these cultures are then recovered in order to quantitatively determine the nitrogenous derivatives and TNF-α. Likewise, during stimulation by IgE, the cells are first activated by IL-4, so as to induce the CD23, and are then subsequently cultured and stimulated by the IgE-containing immune complexes for 3 to 5 days before recovering the different supernatants. In all the cases, cellular viability is achieved on conclusion of these cultures. In the specific case of macrophages, a long-term (7 to 12 days) viability study was carried out, so as to determine the protective effects of these products. Quantitative determination of the nitrogenous derivatives is carried out using the Gries approach and the TNF level is measured by using quantitative determination kits from Medgénix (Fleurus, Belgium).

2. Results

2.1. Effect of a Ginkgo biloba extract on the keratino-cytes and the macrophages stimulated by IFN-γ+ LPS

Dry Ginkgo biloba leaves were subjected to continuous extraction by an acetone/water mixture under vacuum and then several stages of removal of solvent as well as of chlorophyll, lipids, waxes, lectins and of certain substances result in an extract subsequently denoted by H37.

It exists in the form of a fine powder corresponding to the following specifications:

residual solvents	
ethanol	<3%
acetone	<0.1%
butanol	<0.1%
ethyl acetate	<0.1%
sulphated ash	<1.5%
water content	<3%
pro-anthocyanidins	<5%
terpenes	<0.5%
ginkgolic acid	<10 ppm
heavy metals	<20 ppm
flavone heterosides	32 ± 3%

It is 6% (w/w) soluble in PEG 400 and 4% (w/v) soluble in 90° ethanol.

In this study, the product H37 (10 mg/ml) is added 30 min before stimulation by IFN-γ+ LPS. This product showed no cytotoxic activity.

TABLE 1A

Production of nitro derivatives (NO_2^- μM) after stimulation by IFN-γ + LPS +/- 10 mg/ml H37

Cells		Expt-1	Expt-2	Expt-3	Expt-4
Macrophages		11(5)*	15(5)	5(3)	2(9)
	+H37	7(4)	8(4)	2(2)	2(2)
Keratinocytes		12(15)	17(3)	23(12)	13(5)
	+ H37	7(6)	7(3)	8(11)	6(4)

*The values between brackets are those of cells which have not been stimulated by IFN-γ + LPS

TABLE 1B

Production of TNF (pg/ml) after stimulation by IFN-γ + LPS +/- 10 mg/ml H37.

Cells		Expt-1	Expt-2	Expt-3	Expt-4
Macrophages		755(ND)*	1250(155)	998(55)	1510(ND)
	+H37	605(ND)	1120(75)	895(50)	1315(ND)
Keratinocytes		187(ND)	173(ND)	208(ND)	135(ND)
	+ H37	168(ND)	165(ND)	112(ND)	105(ND)

*The values between brackets are those of cells which have not been stimulated by IFN-γ + LPS, ND = non-detectable.

Through these experiments, it appears that the macrophages stimulated by IFN-γ+ LPS do not produce nitro derivatives to a significant extent whereas the keratinocytes produce it reproducibly. In fact, it has recently been demonstrated that, during such a stimulation, the macrophages produce a truncated NO synthase which could have a significant decrease in its activity, which is apparently not the case for the keratinocytes.

In the keratinocytes, H37 inhibits the production of NO after stimulation.

The product H37 exhibits a slight "anti-inflammatory" activity. Moreover, on evaluating the dose effect of H37 on this production by the keratinocytes, it is shown that the maximum effect is observed at 10 mg/ml.

In addition, H37 protects the macrophage cells from the cell death induced by radical products. The fact that the stimulated macrophages do not produce significant amounts of nitro derivatives does not rule out the fact that these cells are not subjected to an oxidative shock which can result in cell death.

This is objectivized by comparisons of the effects on the long-term cell viability at 10 days or with the short-term cultures (2 days). It appears that H37, at 10 mg/ml, protects the macrophage cells from the cell death induced most of the time by the radical products.

TABLE 2

Effect of H37 on the viability of the macrophages

Macrophages + IFN/LPS	% of viable cells at D2	% of viable cells at D10
Medium	85 ± 2	55 ± 7
+ H37	88 ± 3	80 ± 2

2.2. Effect of the product H37 on the macrophages and the keratinocytes stimulated by IL-4.

The cells are stimulated for 48 h in the presence of IL-4 (10 ng/ml), so as to induce the receptor with a low affinity for the IgEs (CD23) at their surface. On completion of this culturing period, 30 to 80% of the keratinocytes and of the macrophages express CD23. The individual variations are in no case the reflection of a different allergic situation between these individuals. Whatever the situation, in this induction phase, the tested product does not modify this induction of CD23; in fact, a decrease of less than 5% cannot be observed (n=8).

TABLE 3

Induction of the expression of CD23 by the different cells stimulated by IL-4 in the presence or in the absence of 10 mg/ml H37

Cells	Medium	+ IL-4
Macrophages	<5%	45 +/- 4
+H37	<5%	41 +/- 2
Keratinocytes	ND	55 +/- 7
+H37	ND	51 +/- 4

*The cells are stimulated for 48 h in the presence or in the absence of 10 ng/ml of IL-4 and in the presence or in the absence of the different products, ND = non-detectable.

After the CD23 has been taken up by IgE-containing immune complexes, the production of a large number of mediators and cytokines (in particular TNF) and of products resulting from the oxidative metabolism, such as nitrogenous derivatives, is induced. This stimulation redefines in vitro an allergic-type inflammatory reaction.

In-this case, the results observed are in every respect comparable with those obtained with IFN-γ and LPS, which tends to demonstrate that H37 exhibits certain anti-inflammatory activities (non-specific and allergic), probably via its ability to regulate the oxidizing abilities of the "inflamed" cells. The results obtained are summarized in the following two tables:

TABLE 4A

Production of nitro derivatives (NO_2^- μM) after stimulation by IL-4 +/- 10 mg/ml H37

Cells		Expt-1	Expt-2	Expt-3	Expt-4
Macrophages		25(5)*	30(2)	55(11)	15(2)
	+H37	15(2)	17(75)	21(50)	6(2)
Keratinocytes		17(13)	13(3)	23(12)	13(5)
	+ H37	12(11)	8(2)	10(10)	8(6)

*The values between brackets are those of cells which have not been stimulated by the IgE-containing immune complexes.

The product H37 exhibits a good ability to inhibit the production of nitro derivatives by the macrophages and the keratinocytes stimulated by IL-4.

TABLE 4B

Production of TNF (pg/ml) after stimulation by IL-4 +/- 10 mg/ml H37

Cells		Expt-1	Expt-2	Expt-3	Expt-4
Macrophages		975 (105) *	275 (35)	455 (40)	310 (89)
	+H37	850 (105)	215 (25)	365 (25)	275 (87)
Keratino-		185 (ND)	158 (ND)	315 (35)	308 (ND)
cytes	+ H37	155 (ND)	120 (ND)	245 (30)	276 (ND)

* The values between brackets are those of cells which have not been stimulated by the IgE-containing immune complexes, ND = non-detectable.

The product H37 induces a slight decrease in the production of TFN-α by the macrophages and the keratinocytes stimulated by IL-4.

Just as during the non-specific stimulation, it appears that H37 increases the long-term viability of the macrophages and of the keratinocytes stimulated by the IgE-containing immune complexes, which, again, suggests very strongly that the product H37 exerts its slight anti-inflammatory activity via an anti-oxidizing activity with respect to the target cells.

It therefore appears that the product H37 exhibits an anti-inflammatory activity (allergic or non-allergic). This characteristic is very important because the seriousness of the inflammatory responses, whether or not of allergic origin, results from an imbalance in the oxidative metabolism of these cells. It is in particular this imbalance which is the source, at least in part, of the regulation of the immunological phenomena associated with these reactions: this is the case for specific allergen reactions and for the production of cytokines.

2.3. Effect of the products K17 and K18 on the keratinocytes and the macrophages stimulated by IFN-γ+ LPS

Drieline is denoted by K17. Drieline is a poly-β(1→3)-glucopyranose purified from *Saccharomyces cerevisiae* yeast membranes; it is in solution in a water/sorbitol mixture.

Carboxymethyl-β-glucan (sold under the trade name CM Glucan® by the company Arnaud) is denoted by K18.

In this study, the products (10 mg/ml or 1/100 v/v) are added 30 min before stimulation by IFN-γ+ LPS. In none of the cases have these products shown a cytotoxic activity.

TABLE 5A

Production of nitro derivatives (NO_2^- in μM) after stimulation by IFN-γ + LPS +/- 10 mg/ml of the products K17 and K18

Cells		Expt-1	Expt-2	Expt-3	Expt-4
Macrophages		13(2)*	8(5)	9(6)	3(2)
	+K17	5(2)	2(1)	7(1.5)	2(2)
	+K18	6(1)	4(1)	5(1)	1(2)
Keratinocytes		25(2)*	28(5)	19(6)	13(2)
	+K17	15(2)	16(1)	15(1)	8(2)
	+K18	13(1)	14(1)	11(1)	7(1)

*The values between brackets are those of cells which have not been stimulated by IFN-γ + LPS.

The products K17 and K18 have a high ability to inhibit the production of nitro derivatives by the macrophages and the keratinocytes stimulated by IFN-γ and LPS.

TABLE 5B

Production of TNF (pg/ml) after stimulation by IFN-γ + LPS +/- or 10 mg/ml of the products K17 and K18

Cells		Expt-1	Expt-2	Expt-3	Expt-4
Macrophages		612(ND)*	920(155)	903(55)	700(ND)
	+K17	605(ND)	902(95)	970(45)	695(ND)
	+K18	121(ND)	320(125)	512(20)	333(ND)
Keratinocytes		205(ND)	138(ND)	145(ND)	108(ND)
	+K17	125(ND)	98(95)	100(ND)	70(ND)
	+K18	130(ND)	95(ND)	85(ND)	82(ND)

*The values between brackets are those cells which have not been stimulated by IFN-γ + LPS, ND = non-dectectable.

The production of TNF-α by the macrophages and the keratinocytes stimulated by IFN-γ+ LPS is also detrimentally affected in the presence of the different products in a way comparable with that observed for the nitro derivatives. The products K17 and K18 efficiently inhibit the production of TNF.

2.4. Effect of the products K17 and K18 on the macrophages and the keratinocytes stimulated by IL-4.

The cells are stimulated for 48 h in the presence of IL-4 (10 mg/ml), so as to induce the receptor with a low affinity for the IgEs (CD23) at their surface. On completion of this culturing period, 30 to 80% of the keratinocytes and of the macrophages express CD23. The individual variations are in no case the reflection of a different allergic situation between these individuals. Whatever the situation, in this induction phase, none of the tested products modifies this induction of CD23; in fact, a decrease of less than 5% cannot be observed (n=8).

After the CD23 has been taken up by IgE-containing immune complexes, the production of a large number of mediators and cytokines (in particular TNF) and of products resulting from the oxidative metabolism, such as nitrogenous derivatives, is induced. This stimulation redefines in vitro an allergic-type inflammatory reaction.

TABLE 6A

Production of nitro derivatives (NO_2^- in μM) after stimulation by IgE-containing immune complexes (IL-4) +/- 10 6mg/ml of the products K17 and K18

Cells		Expt-1	Expt-2	Expt-3	Expt-4
Macrophages		15(5)*	18(3)	25(11)	27(3)
	+K17	16(3)	17(6)	19(7)	30(6)
	+K18	7(2)	6(4)	10(2)	7(2)
Keratinocytes		19(5)*	22(1)	13(1)	7(1)
	+K17	16(3)	20(3)	14(2)	7(6)
	+K18	4(2)	7(4)	9(2)	3(2)

*The values between brackets are those of cells which have not been stimulated by IgE-containing immune complexes.

The product K18 exhibits an inhibitory activity on the generation of nitro derivatives by the keratino-cytes and the macrophages stimulated by IL-4.

TABLE 6B

Production of TNF (pg/ml) after stimulation by IL-4 +/- K17 and K18

Cells		Expt-1	Expt-2	Expt-3	Expt-4
Macrophages		908(78)*	135(40)	508(45)	712(58)
	+K17	917(45)	102(41)	510(41)	700(32)
	+K18	524(59)	98(35)	420(32)	333(25)
Keratinocytes		198(31)*	105(10)	128(10)	132(15)
	+K17	185(35)	111(31)	120(32)	132(40)
	+K18	95(23)	60(35)	25(12)	35(12)

*The values between brackets are those of cells which have not been stimulated by IgE-containing immune complexes, ND = non-detectable.

The product K18 exhibits an inhibitory activity on the generation of TNF by the macrophages and the kertinocytes stimulated by IL-4.

It therefore appears that K18 possesses a non-specific and allergic-type anti-inflammatory activity whereas the product K17 only has a non-specific anti-inflammatory activity.

Consequently, the effects of the product K18 were evaluated as a function of the dose. The results are illustrated in FIG. 1.

K18 therefore inhibits, in a dose-dependent way, the generation of nitro derivatives and also of TNF. The results thus obtained demonstrate that K18 exhibits a generally advantageous anti-inflammatory activity and that this activity is similar to that of H37.

EXAMPLE 2

Demonstration of an activity synergy between CM-β-glucan (K18) and ginkgo extract (H37)

The anti-inflammatory activities of K18 and H37 and of their combination respectively are determined.

The tests are carried out in a keratinocyte model, as indicated in Example 1 (Materials and Methods) after stimulation, on the one hand, by an IFN-γ+ LPS combination and, on the other hand, by IL-4 and IgE-containing immune complexes.

As shown in FIG. 2, the products K18 and H37 act in synergy in their anti-inflammatory functions.

It should be recalled that this anti-inflammatory activity covers the non-specific and allergic anti-inflammatory activity.

EXAMPLE 3

Analysis of the prevention of detrimental cutaneous changes obtained by UV A and UV B irradiation of human skin

Organ cultures are produced according to the following protocol: 10 skin fragments from different donors (source:plastic surgery) are placed in inserts which are themselves positioned over culture wells. Culture medium (antibiotics, FCS) is added to the bottom of the wells, passage between the two compartments being achieved by slow diffusion via a porous membrane (0.45 μm).

Before each irradiation, each cosmetic cream (2 mg/cm^2) is deposited directly on the skin for 2 hours (control skins without treatment will be analysed in parallel). The 3 creams and the excipient are renewed three times per week on the skins:

cream 1: 0.5% CM-glucan

cream 2: 0.05% Ginkgo biloba

cream 3: CM-glucan+Ginkgo biloba extract (H37)

cream 4: excipient (Carbopol placebo)

After having removed the surplus cream, the skin is then irradiated with 12 J/cm^2 of UV A and 6 J/cm^2 of UV B (Vilber Lourmat T40 M lamp), equivalent to 20 DEM, doses determined by a preliminary study which make it possible to rapidly obtain lesions at the level of the epidermis and dermis with, in particular, detrimental changes in the collagen and elastic fibres. These doses are, moreover, equivalent to the doses used for the photopatch tests and to the doses used in hairless murine models for generating sunburn cells.

Irradiation is carried out every other day. Three exposure sessions are carried out and then the skin fragments are collected for the following analyses.

The production of oxygen derivatives, such as nitric oxide (NO), shows attack by UV radiation.

The possible protection contributed by the creams will be quantified by evaluating the decrease in the amount of nitrites and the increase in SOD.

1) Quantitative determination of nitric oxide and of nitrites

Nitric oxide, NO, is an important physiological mediator, not only as vasodilator and neurotransmitter but also as pro-inflammatory agent. Its synthesis is mediated by an enzyme, NO synthase, which is expressed by many cell types and in particular keratinocytes, when they are activated.

NO, obtained by oxidation of L-arginine by NO synthase, is an unstable product which is rapidly degraded to nitrites (NO_2) and nitrates (NO^3). It is the spectrophotometric quantitative determination of the nitrites in the culture supernatant in the presence of Griess's reagent which reveals the NO synthase activity.

The results are reported in the table below.

Quantitative determination of the nitrites

	(nmol/ml)	% of protection
Skin treated with cream 1	21.6 ± 7.3	14.7% ± 8.2
Skin treated with cream 2	21.4 ± 3.6	13.5% ± 5.8
Skin treated with cream 3	16.4 ± 2.9*	33.8% ± 2.3*
Skin treated with cream 4	24.9 ± 5.3	

*Statistically significant result ($p < 0.05$; Student's test)

The percentage of protection was calculated in the following way: (A-B/A)x100 where A is the result with cream No. 4 and B the result which cream 1, 2 or 3.

The skins treated with creams 1 and 2 exhibit a slight decrease (not significant) in the production of nitrites. The greatest decrease is obtained with skins treated with cream 3, a difference which is statistically significant with respect to the excipient. Calculation of the percentage of protection confirms these results, cream 3 having in particular a protection of 34%.

2) Quantitative determination of SOD

Attack by U.V. radiation is reflected by a decrease in the level of SOD.

The activity of superoxide dismutase is determined by the technique of McCord and Fridovich. Briefly, superoxide anions are generated by the action of xanthine oxidase on xanthine. The SOD present in the samples can then inhibit the reduction of cytochrome C by these superoxide anoins. The activity of the SOD is related to the amount of reduced cytochrome C remaining in the reaction medium.

The results are expressed by percentages of inhibition with respect to the excipient (cream No. 4): the SOD hydrolyses a portion of the free radicals generated by the U.V. attack and the xanthine/xanthine oxidase system. Thus, the decrease in the optical density (proportional to the amount of free radicals) will make it possible directly to quantify the level of SOD.

Quantitative determination of SOD

	% of inhibition
Skin treated with cream 1	11.1% ± 3.4
Skin treated with cream 2	7.04% ± 2.9
Skin treated with cream 3	15.1% ± 3.3*

*Statistically significant result ($p < 0.05$: Student's test)

With respect to the excipient, the skins treated with creams 1 and 2 show a slight protection (not significant) against the decrease in the SOD activity induced by UV radiation. This protection is greater with the skins treated with cream 3, a difference which is statistically significant with respect to the excipient.

Conclusion

Quantitative determination of the nitrites has demonstrated, for skins treated with cream No. 3, a significant decrease in their amount with respect to the excipient. These results make it possible to envisage the protective activity of cream No. 3 with respect to the detrimental dermal changes generated by inflammatory components. Skins treated with creams 1 and 2 have only a tendency towards protection. There therefore exists a synergy between the components of cream No. 3.

Quantitative determination of SOD seems to confirm this analysis with protection of skins treated with cream No. 3 with respect to detrimental radical changes generated by U.V. radiation. Skins treated with creams 1 and 2 have only a tendency towards protection, more marked in the case of cream No. 1.

EXAMPLE 4

Compositions containing combinations according to the invention

	%
A) Formulation with depigmenting agents	
Water	70.965
Octyl methoxycinnamate	6.000
Glyceryl stearate/PEG-100 stearate	5.000
Glycerol	5.000
C_{12}–C_{15} alkyl benzoate	4.000
Petrolatum	1.500
Cetyl palmitate	1.000
Cetyl alcohol	1.000
Stearyl alcohol	0.500
Sodium sulphite	0.025
Sodium disulphite	0.025
Hydroquinone	2.000
Citric acid	0.15
Carbomer	0.300
Tocopheryl acetate	0.100
Phenoxyethanol	0.730
Methylparaben	0.200
Propylparaben	0.070
Sodium hydroxide	0.135
Disodium EDTA	0.200
β-Glucan	1.0
Ginkgo biloba extract	0.1
B) Formulation with retinol	
Water	56.42
Cetearyl octanoate	9.00
Octyl methoxycinnamate	8.00
Lactose	5.00

-continued

	%
Glycerol	5.00
Hydrogenated groundnut oil	5.00
Glyceryl polymetbacrylate	3.45
Butylmetboxydibenzoylmethane	1.50
Isopropyl myristate	1.00
Hydrogenated lecithin	1.00
β-Glucan	1.00
Ammonium hydroxide	0.75
Phenoxyethanol	0.73
C_{10}–C_{30} Alkyl acrylate copolymer/acrylates	0.50
Poloxamer 407	0.50
Tocopheryl acetate	0.50
Methylparaben	0.20
Ginkgo biloba extract	0.10
Carbomer	0.10
BHT	0.10
Propylparaben	0.07
Propylene glycol	0.05
Retinol	0.03
	100.00

C) Formulation with retinol

Water	69.689
Octyl hydroxystearate	6.2942
Glycerol	4.0000
Ceteareth-20/stearyl alcohol	3.0000
Ceteateth-20/cetearyl alcohol	3.0000
Glyceryl distearate	2.8000
Dimethicone	2.5000
C_{12}–C_{15} Alkyl lactate	1.5000
Steareth-10	1.4000
Cholesterol	1.0000
Acetylated lanolin alcobol/cetyl acetate	1.0000
Polysorbate 80	0.7000
Sodium citrate	0.5160
C_{13}–C_{14} Isoparaffin/lauretb-7	0.5000
Stearyl alcobol	0.5000
Polysorbate 20/retinol	0.1058
BHT	0.1000
Methylparaben	0.2000
Fragrance	0.0500
Propylparaben	0.0300
Citric acid	0.0150
Ginkgo biloba extract	0.1
Panthenol	1.0
	100.

D) Formulation with tretinoin

Tretinoin	0.05 g
β-Glucan	0.50 g
Ginkgo biloba extract	0.10 g
Light liquid paraffin	25.00 g
Non-crystallizable 70 percent sorbitol solution	5.00 g
Hydroxyoctacosanyl bydroxystearate	5.00 g
Methoxymacrogol 22/dodecyl glycol copolymer	5.00 g
Macrogol 45/dodecyl glycol copolymer	3.00 g
Stearoxytrimethylsilane and stearyl alcobol	1.00 g
Dimethcone	1.00 g
Fragrance	0.25 g
Methyl para-hydroxybenzoate	0.20 g
Sodium edetate	0.10 g
Quaternium 15	0.10 g
Butylated hydroxytoluene	0.10 g
Citric ncid monohydrnte	0.10 g
Purified water	53.495 g

What is claimed is:

1. A method for treating sensitive or allergic skin by topically applying to said skin a composition comprising at least two compounds chosen from components having at least two activities selected from the group consisting of: a) anti-radical, b) anti-inflammatory and c) anti-allergic activity, wherein said composition comprises compounds having anti-radical, anti-inflammatory and anti-allergic activity.

2. A method according to claim 1 wherein said compounds exhibiting an anti-radical activity are chosen from the group consisting of free-radical scavengers, anti-lipoperoxidants and stimulants of the endogenous production of the enzymes which degrade free radicals or a combination thereof.

3. A method according to claim 1 wherein said compounds exhibiting an anti-inflammatory activity are chosen from the group consisting of prostaglandin inhibitors, inhibitors of cytokine production and inhibitors of leukotriene production or a combination thereof.

4. A method according to claim 1 wherein said compounds exhibiting anti-allergic activity are chosen from the group consisting of inhibitors of lymphocyte proliferation, inhibitors of the internalization of HLA receptors and inhibitors of cytokine production or a combination thereof.

5. A method according to claim 1 comprising the topical application of said composition to the skin to inhibit the synthesis or the expression of neuromediators by cutaneous cells.

6. A method according to claim 1 wherein at least one compound is chosen from the following group: Ginkgo biloba and its extracts, iramine, D-panthenol, β-sitosterol, modulene, α-tocopherol and its derivatives, α-tocopherol phosphate, β-glucan and its derivatives, eicosapentanoic acid, 18 β-glycyrrhetinic acid, glycyrrhetinic acid monoglucoronide, stearyl glycyrrhetinate, Scutellaria extract, lactoferrin, green tea extract, vitamin C glutathione, epidermal thymus factor, imidazole derivatives, triazole derivatives and lipacid, provided that said composition excludes the combination of vitamin E and Scutellaria extract.

7. A method according to claim 6, wherein at least two components are chosen from the following group: Ginkgo biloba and its extracts, iramine, D-panthenol, β-sitosterol, modulene, α-tocopherol and its derivatives, α-tocopherol phosphate, β-glucan and its derivatives, eicosapentanoic acid, 18 β-glycyrrhetinic acid, glycyrrhetinic acid monoglucoronide, stearyl glycyrrhetinate, Scutellaria extract, lactoferrin, green tea extract, vitamin C glutathione, epidermal thymusfactor, imidazole derivatives, triazole derivatives and lipacid,

provided that said composition excludes the combination of vitamin E and Scutellaria extract.

8. A method according to claim 7 comprising the topical application of a composition comprising at least one of the combinations selected from the group consisting of: α-tocopherol/Ginkgo biloba extract, carboxymethyl-β-glucan/Ginkgo biloba extract, β-sitosterol/D-panthenol, drieline/lactoferrin and panthenol/green tea extract.

9. A composition with hypoallergenic or immunomodulatory activity or which is intended for the treatment of sensitive skin made in accordance with the process comprising the steps of:

a) selecting compounds which exhibit a least one anti-inflammatory, anti-radical and/or anti-allergic activity, at least two of such compounds exhibiting at least two different activities;

b) combining said compounds and determining whether at least one of the activities is potentiated by the combination of said compounds;

c) selecting at least one of the combinations of compounds in which said activities is potentiated; and

d) mixing at least one of the selected combinations with dermatiologically or cosmetologically acceptable excipients, in order to obtain a composition having

hypoallergenic or immunomodulatory activity provided that said composition excludes the combination of vitamin E and Scutellaria extract;

wherein said composition comprises at least on component chosen from the group consisting of Ginkgo biloba and its extracts, iramine, D-panthenol, β-sitosterol, modulene, α-tocopherol and its derivatives, α-tocopherol phosphate, β-glucan and its derivatives, eicosapentanoic acid, 18 β-glycerrhetinic acid, glycyrrhetinic acid monoglucoronide, stearyl glycyrrhetinate, Scutellaria extract, lactoferrin, green tea extract, vitamin C glutathione, epidermal thymusfactor, imidazole derivatives, triazole derivatives and lipacid, provided that said composition excludes the combination of vitamin E and Scutellaria extract, wherein said composition comprises a concentration of Ginkgo biloba extract containing a terpene concentration which is less than 1% w/w of dry matter in an amount of from about 0.001% to about 10% w/w and β-glucan which is substituted by carboxymethyl groups.

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[54] **PHARMACEUTICAL COMPOSITIONS AND METHODS FOR PROTECTING AND TREATING SUN DAMAGED SKIN**

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[52] **U.S. Cl.** **424/59**; 424/60; 424/400; 424/401

[58] **Field of Search** 424/59, 60, 400, 424/401

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[57] **ABSTRACT**

This invention relates to a pharmaceutical composition for the protection and prevention of skin damage to a patient resulting from exposure to sunlight having at least one antioxidant component in an amount sufficient to inhibit the formation of free radicals; at least one anti-inflammatory component in an amount sufficient to substantially inhibit the inflammation associated with exposure to sunlight; and at least one immunity boosting component to enhance the patient's immune response. In a preferred form, the composition also includes a cysteine component, a magnesium component, a manganese component, a copper component, a selenium component, and a carotenoid component. In a more preferred form the invention also includes wild yam root, wild yam extract, yellow dock, bupleurum, poria cocos, gentian root, myrrh gum, hawthorn berry extract, and rosemary extract. The invention also relates to a method for protecting skin from damage caused by exposure to sunlight by administering the pharmaceutical composition in an amount therapeutically effective in increasing the sun protection factor of the skin.

21 Claims, No Drawings

PHARMACEUTICAL COMPOSITIONS AND METHODS FOR PROTECTING AND TREATING SUN DAMAGED SKIN

TECHNICAL FIELD

This invention relates to pharmaceutical compositions, as well as methods, to protect skin from the armful effects of sunlight.

BACKGROUND OF THE INVENTION

The skin is the most environmentally-stressed organ in mammals, particularly in humans. Not only is the skin subjected to toxic chemicals and hostile environments, but it also is the only organ directly exposed to Ultraviolet ("UV") light in the presence of oxygen. [See, e.g., P. Mayer, et al., *Cosmetic & Toiletries,* 108:99–109 (February 1993)]. Lengthy exposure of the skin to UV light typically damages the skin, resulting, in sunburn, photoaging and carcinogenesis.

UV light exposure in the presence of oxygen results in the creation of free radicals. In the skin, these radicals frequently trigger the release of inflammatory mediators, commonly manifested as sun burn; cytoskeletal alterations, breaking down the collagen in the skin; and may also result in structural DNA changes, such as DNA strand breaks and dimer formation. [K. Werninghaus, et al., *Arch Dermatol.,* 130:1257–1261 (October 1994)]. The body attempts to neutralize the free radicals generated by UV light through the use of antioxidants. Antioxidants are commonly found in two forms-enzymatic and non-enzymatic. Superoxide dismutase (SOD), catalase, and glutathione peroxidase are natural enzymatic antioxidants used by the body. SOD accelerates the spontaneous reduction of superoxide free radicals into peroxides and oxygen. Catalase then further decomposes hydrogen peroxide into water and oxygen. Finally, the glutathione peroxidase reduces both hydrogen peroxide and free organic hydroperoxides. Non-enzymatic antioxidants, such as Vitamin E (tocopherol), Vitamin A (beta-carotene), and Vitamin C (ascorbic acid) have been individually applied to assist the skin in scavenging free radicals and neutralizing the harmful effects of UV light. [P. Pugliese, "A Brief Introduction to Free Radicals and Oxygen Stress," Paper presented at International Conference of Aesthetics and Dermatology, Los Angeles, (February 1991)]. Conventional skin protection efforts typically attempt to either shield the skin from UV light to prevent the production of free radicals, or provide additional agents capable of neutralizing the free radicals.

Topical applications are one such effort well known in the art that shields the skin from the sun's harmful effects. These sun-screens often are water- or oil-based lotions or ointments that incorporate photo-protectant materials such as titanium and zinc oxide. [J. Weiss, *Skin,* 16–23 (March/April 1996)]. Although the most widely used form of protection against exposure to sunlight, these topical applications suffer from several drawbacks. First, large amounts of photo-protective materials are incorporated into the topical applications, some of which have recently become suspect of having toxicity under these conditions or otherwise being harmful. Furthermore, the effectiveness of such topical applications is dependent upon a constant and uniform coverage of the skin, which is often difficult to obtain. Many individuals fail to use these topical sunscreens on a regular or continuing basis, as is required under prolonged UV exposure. Finally, sunscreens do not provide good protection for all types of UV light. [Id.].

In addition, various conventional supplements have attempted to boost the body's natural antioxidant activity using vitamins, minerals, and herbs. Vitamin C, for example, is believed to reduce sun damage, and vitamin E has been used topically as an anti-inflammatory agent and for UV-ray protection of cells. Also, carotenoids may have usefulness as antioxidants, protecting against both free radicals and singlet oxygen, a highly reactive, diamagnetic excited state of dioxygen. Moreover, it is thought that minerals are typically needed to maintain the effectiveness of the body's enzymatic antioxidants. Both copper and zinc are thought to be necessary in the proper functioning of SOD. [G. La Ruche & J. -P. Cesarini, *Photodermatol Photoimmunol Photomed.,* 8:232–235 (1991)]. Manganese is believed to be a cofactor in the mitochondrial form of SOD. Also, selenium is thought to be necessary to glutathione peroxidase, an important antioxidant found naturally in the body. Unfortunately, few experiments into the skin-protecting effects of these antioxidants have provided conclusive results.

In particular, a study that orally administered vitamin E supplements to participants and then tested their response to the sun found that Vitamin E did not mitigate the UV damage, despite the fact that the subjects were given thirteen times the recommended daily allowance. [K. Werninghaus, et al., *Arch. Dermatol.,* 130:1257–1261 (October 1994)]. Furthermore, beta-carotene has been reported to have beneficial effects in some studies, but has had no effect in others. Finally, another study noted the photo-protective effect of the oral administration of butylated hydroxy toluene, but little effect was shown using vitamins C or E.

Certain herbs have also been found helpful in protecting the skin from the sun's harmful effects. Herb extracts such as burdock root, echinacea, yellow dock root and grape seeds posses detoxifying properties that have been individually applied to help the body eliminate harmful free radicals. Burdock root contains the active ingredient inulin, and is useful in treating cankerous skin conditions, as well as inflammation. Echinacoside and caffeoyl derivatives present in echinacea act as potent antioxidants, which protect the skin when applied topically. [R. Facino, et al., *Planta Med.* 61:510–514 (1995)]. Yellow dock root contains the active constituent chrysarobin, which has been used in the treatment of chronic skin diseases, such as eczema, leprosy, psoriasis, and cancer. [M. Tierra, "Planetary Herbology," p. 194 (1988)]. Potent bioflavanoids, known as oligomeric proanthocyanidins (OPC's), are found in grape seeds. These OPC's are thought to be potent antioxidants possessing 20 times the antioxidant power of vitamin C and 50 times the antioxidant power of vitamin E. These herbs have been individually used both topically and orally to protect the skin from various afflictions.

Other studies have attempted to demonstrate the synergistic effect of a mixture of antioxidants. In one study, the subjects were given selenium and copper along with a vitamin supplement of vitamin A and E. [G. La Ruche & J. P. Cesarini, *Photodermatol Photoimmunol Photomed.,* 8:232–235 (1991)]. Although the supplements did protect the skin cells to some extent against ultraviolet-induced cell damage, they did not prevent light-induced erythema, redness.

Also, U.S. Pat. No. 5,290,605, discloses a soft drink that provides protection against sun damage. This drink contains a mixture of carotenoids, optionally together with vitamin C, vitamin E, or other effective antioxidants. The above antioxidants are limited to an amount which does not exceed ten vitamin A RDA equivalents of provitamin A per liter of drink.

Nutritional supplements such as Source Naturals' PYCNOGENOL® COMPLEX™ provide a variety of vitamins, minerals and herb extracts to protect the body against free radicals. In particular, the PYCNOGENOL® COMPLEX™ contains pycnogenol, proanthodyn, quercetin, Ginkgo Biloha extract, Green Tea extract, Bilberry extract, Silymarin, Tumeric extract, Hawthorn Berry extract, Rosemary extract, vitamin C (in the form of zinc and magnesium ascorbates), and magnesium.

Also, an herbal supplement and nutritional suggestions for the maintenance of the skin are disclosed in "The Scientific Validation of Herbal Medicine" by Daniel B. Mowrey, Ph.D. (p.247–251 1986). The herbal supplement consists of extracts of chaparral, dandelion root, burdock root, licorice root, echinacea, yellow dock root, kelp and cayenne. The reference also suggests the use of the following nutritional supplements: vitamin A, vitamin B_1, vitamin B_2, vitamin B_6, a vitamin B complex, vitamin C, vitamin D, vitamin E, niacinamide, pantothenic acid, para-aminobenzoic acid, biotin, choline, inositol, folic acid, zinc, calcium, magnesium, and potassium.

Although the above supplements and studies provide UV-protection for the skin, none provide for all aspects of an antioxidant supplement necessary to protect the skin from damage resulting from exposure to sunlight. It is desired that a composition be formulated that contains the proper ratio of vitamins, minerals and herbal components to more effectively and advantageously provide protection to the sun or other sources of UV-damage.

SUMMARY OF THE INVENTION

The invention relates to a pharmaceutical composition for the prevention and treatment of skin damage resulting from exposure to light in a patient. The pharmaceutical composition has at least one primary antioxidant component in an amount sufficient to reduce free radicals; at least one anti-inflammatory component in an amount sufficient to reduce inflammation of the skin; and at least one immunity boosting component in an amount sufficient to enhance the patient's immune response to prevent or facilitate repair of damaged skin.

In a preferred embodiment, the primary antioxidant component is present in about 5 to 50 weight percent, the anti-inflammatory component is present in about 5 to 40 weight percent, and the immunity boosting component is present in about 1 to 20 weight percent of the composition.

In one embodiment, the primary antioxidant component comprises at least one of a catechin-based preparation, a vitamin A source, a ginkgo biloba extract, a silymarin source, a quercetin compound, and a vitamin C source.

In a preferred embodiment, the primary antioxidant component comprises at least a proanthanol or proanthocyanidin as the catechin-based preparation, vitamin A palmitate as the vitamin A source, milk thistle extract as the silymarin source, quercetin dihydrate as the quercetin compound, and an ascorbic acid compound or a salt or ester thereof as the vitamin C source.

In a more preferred embodiment, the primary antioxidant component comprises proanthocyanidin present in about 0.1 to 5 weight percent, vitamin A palmitate present in about 0.1 to 5 weight percent, ginkgo biloba extract present in about 0.01 to 3 weight percent, quercetin dihydrate present in about 1 to 20 weight percent, ascorbic acid present in about 5 to 50 weight percent, and milk thistle extract present in about 1 to 20 weight percent.

In another embodiment, the anti-inflammatory component comprises a vitamin E source, a zinc compound or a pharmaceutically acceptable salt thereof.

In a preferred embodiment, the vitamin E source is a sulfate or succinate complex of vitamin E and the zinc compound is a complex of zinc and an amino acid. In a more preferred embodiment, the vitamin E source is D-alpha tocopherol acid succinate present in about 5 to 40 weight percent, and the zinc compound is zinc monomethinone present in about 1 to 12 weight percent, wherein the zinc is preferably present in about 10 to 30 weight percent of the complex.

In another embodiment, the immunity boosting component comprises at least one of echinacea, an echinacea extract, and golden seal.

In one embodiment, the composition further comprises a pharmaceutically acceptable carrier or excipient.

In yet another embodiment, the pharmaceutical composition further has one or more of a cysteine component, a magnesium component, manganese component, a copper component, a selenium component, or a carotenoid component.

In a preferred embodiment, the cysteine component is N-acetyl cysteine and is present in about 1 to 10 weight percent, the magnesium component is magnesium ascorbate and is present in about 1 to 10 weight percent, wherein the magnesium is present in about 10 to 30 weight percent of the complex, the manganese component is manganese ascorbate and is present in about 0.5 to 10 weight percent, wherein manganese is present in about 5 to 20 weight percent of the complex, the copper component is copper sebacate and is present in about 0.01 to 5 weight percent, wherein the copper is present in about 5 to 20 weight percent of the complex, and the carotenoid component is beta carotene and is present in about 0.1 to 5 weight percent.

In another embodiment, the pharmaceutical composition also possesses at least one of the wild yam root, wild yam extract, yellow dock, bupleurum, poria cocos, gentian root, myrrh gum, hawthorn berry extract, and rosemary extract. In a preferred embodiment, the amount of wild yam root, wild yam extract, marshmallow root, hawthorn berry extract, and rosemary extract, when present, is about 0.5 to 8 weight percent each, the amount of yellow dock, when present, is about 1 to 30 weight percent, and the amount of bupleurum, poria cocos, gentian root and myrrh, when present, is about 1 to 20 weight percent each.

The invention further relates to a method for treating and protecting skin from damage caused by the exposure to sunlight, by administering the pharmaceutical composition in a therapeutically effective amount to increase the sun protection factor of the skin. In a preferred embodiment, the composition is administered orally.

In one embodiment, the composition is administered as a tablet or capsule having about 1 mg to 2,000 mg of composition. In a preferred embodiment, the tablet or capsule has about 400 mg to 1,600 mg of composition. In a more preferred embodiment, the tablet or capsule has about 800 mg to 1,200 mg of composition.

In another embodiment, the composition is administered in conjunction with concurrent or subsequent treatment by at least one additional pharmaceutical composition used to treat or protect the skin from damage from the exposure to sunlight. In a preferred embodiment, the additional pharmaceutical composition consists of a sunscreen having at least one of the following active ingredients: titanium dioxide, zinc oxide, talc, red veterinary petrolatum, octyl methoxycinnamate, oxybenzone, octyl salicylate, and para-aminobenzoic acid; a nutritional supplement having at least one of the following: antioxidants, vitamin E, vitamin C, and

carotenoids; and a a topical application having at least one of the following vitamin A, vitamin E, vitamin C, and alpha-hydroxy acids.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

A pharmaceutical formulation for advantageously protecting skin from damage caused by UV sources, such as the sun, has now been discovered. The formulation may be used alone or in conjunction with a sunscreen to provide protection from UV light. The pharmaceutical composition includes an anti-inflammatory component in an amount sufficient to reduce redness and swelling of the skin, an antioxidant is present in an amount sufficient to neutralize free radicals; and an immunity boosting component in an amount sufficient to boost the immune system to facilitate repair of UV-damaged skin. Preferably, the pharmaceutical composition optionally includes a cysteine component, magnesium component, manganese component, carotenoid component, selenium component, and copper component. Most preferably, the pharmaceutical composition also optionally includes at least one herb from the group of yellow dock, bupleurum, poria cocos, gentian root, myrrh gum, hawthorn berry extract, rosemary extract, wild yam root and wild yam extract. The synergistic effect of these pharmaceutical components boosts the sun protection factor (SPF) of known sunscreens by at least about 5 percent, preferably about 10 percent. Also, on its own the oral doses of the pharmaceutical composition provide enhanced protection of the skin against the damaging effects of the sun.

The present pharmaceutical composition advantageously protects the skin from damage resulting from exposure to UV rays, and treats such damaged skin, by providing antioxidants in the form of a catechin-based preparation such as a proanthanol or proanthocyanidin, vitamin C, vitamin A, ginkgo biloba and silymarin. These antioxidants neutralize the free radicals in the skin generated by exposure to UV light.

The pharmaceutical composition includes a vitamin C component, preferably an ascorbic acid, or a pharmaceutically acceptable salt or ester thereof, and more preferably ascorbyl palmitate, dipalmitate L-ascorbate, sodium L-ascorbate-2-sulfate, or an ascorbic salt, such as sodium, potassium, and calcium, or mixtures thereof. When oral formulations of the pharmaceutical composition are used, it is preferred that a non-acidic form of vitamin C be used to reduce the stomach irritation that may occur when using an acidic form. The vitamin C component is present in the pharmaceutical composition in about 5 to 50 weight percent, preferably about 7 to 40 weight percent, and more preferably 10 to 25 weight percent. A unit dose of the vitamin C component is typically about 50 mg to 800 mg, preferably 60 mg to 600 mg, more preferably about 80 mg to 400 mg.

The vitamin A component preferably is vitamin A palmitate present in about 5 to 50 weight percent, more preferably in about 6 to 40 weight percent, most preferably in about 7 to 30 weight percent of the composition.

The catechin-based preparation useful in the pharmaceutical composition provides powerful antioxidants to scavenge free radicals. These antioxidants provide roughly 20 times more antioxidative power than vitamin C and 50 times more antioxidative power than vitamin E. The catechin-based preparation is preferably a proanthanol or a proanthocyanidin, and more preferably a proanthanol, which is commonly obtained as a grape seed extract. The catechin-based preparation is present in about 0.1 to 5 weight percent, preferably about 0.2 to 3 weight percent, and most preferably about 0.3 to 2 weight percent of the composition. A unit dose of catechin-based preparation includes about 1 mg to 20 mg, preferably about 2 mg to 15 mg, and more preferably about 3 mg to 10 mg.

The composition preferably also includes quercetin powder. Preferably, the quercetin powder is typically quercetin dihydrate present in about 1 to 20 weight percent, preferably about 2 to 15 weight percent, and more preferably about 3 to 10 weight percent in the pharmaceutical composition. Other quercetin compounds can be used, if desired.

The silymarin component, which provides an antioxidant component that specifically targets the liver, may also be added to the pharmaceutical composition. Preferably, milk thistle extract, *Silybum marianum*, provides the silymarin for the present invention. The extract itself contains about 70 to 95 weight percent of silymarin. A unit dose of the pharmaceutical composition may include about 10 to 160 mg of the extract, preferably about 20 to 100 mg, and more preferably about 30 mg to 80 mg.

In a more preferable form, Ginkgo Biloba extract is included in the composition, as well. Volatile oils, tannin and resin are the active constituents of the extract. Ginkgo Biloba supplies antioxidants which are understood to target the brain. Ginkgo Biloba is present in about 0.01 to 3 weight percent, preferably about 0.02 to 2 weight percent, and more preferably 0.03 to 1 weight percent in the pharmaceutical composition.

The anti-inflammatory component of the composition prevents and reduces inflammation, including the redness and swelling that typically accompanies sun-damaged skin. Zinc and/or vitamin E assist in reducing the inflammation associated with overexposure to sunlight.

The zinc component of the pharmaceutical composition mitigates the inflammation associated with UV light damage and assists in binding collagen fibers within the skin. Also, zinc is essential to SOD, and thus affects the body in counteracting free radical formation. The zinc component may be any zinc compound or pharmaceutically acceptable salt thereof, but preferably is a zinc complexed with an amino acid, and more preferably is zinc monomethinone, wherein the zinc is typically present in about 10 to 30 weight percent of the complex. The zinc component is present in about 1 to 12 weight percent, preferably 1.5 to 8 weight percent, and more preferably about 2 to 6 weight percent of the pharmaceutical composition. A unit dose of the zinc source is typically about 5 to 100 mg, preferably about 10 to 75 mg, and more preferably about 15 to 60 mg. Although effective in protecting skin from sun damage, increasing the zinc concentration too much in an oral formulation of the pharmaceutical composition may lead to stomach discomfort.

The vitamin E component is preferably a sulfate or succinate vitamin E complex, and more preferably a D-alpha tocopherol acid succinate. The vitamin E component is present in about 5 to 40 weight percent, preferably about 6 to 30 weight percent, and more preferably about 7 to 20 weight percent of the composition.

An immune boosting component is also part of the composition. Immune boosters, such as echinacea and golden seal, facilitate the healing of the sun damaged tissues.

Echinacea and its extract are obtained from the Echinacea family of plants, and these components act as immune boosters. Also, they contain several potent antioxidant compounds, such as echinacoside and caffeoyl derivatives. Echinacea is present in about 1 to 20 weight percent,

preferably about 2 to 15 weight percent, and more preferably about 3 to 10 weight percent of the composition.

An additional immunity boosting component is provided by the Golden Seal, *Hydrastis canaderis*, preferably present in the pharmaceutical composition. Golden Seal is present in about 1 to 20 weight percent, preferably about 2 to 15 weight percent, more preferably about 3 to 10 weight percent of the composition.

Additionally, the present invention more preferably, but optionally, contains the following: a cysteine component, a magnesium component, a manganese component, a carotenoid, a selenium component, and a copper component.

The cysteine component used in the composition is preferably N-acetyl cysteine, present in about 1 to 10 weight percent, preferably about 2 to 8 weight percent, and more preferably about 3 to 6 weight percent of the composition.

The manganese component is the co-factor used by the SOD found in mitochondria. The manganese component may be any manganese compound or pharmaceutically acceptable salt thereof, but preferably is manganese ascorbate or manganese ascorbic acid, wherein the manganese is typically present in about 5 to 20 weight percent of the complex. When complexed with vitamin C, this vitamin C source may be included in the overall percentage of vitamin C in the pharmaceutical composition.

The copper component is also preferably included in the pharmaceutical composition, and may be any copper compound or pharmaceutically acceptable salt thereof, but preferably is copper sebacate, wherein the copper is present in about 5 to 20 weight percent of the copper sebacate. The copper component is present in about 0.01 to 5 weight percent, preferably about 0.02 to 3 weight percent and more preferably about 0.03 to 2 weight percent of the composition. A unit dose of the pharmaceutical composition may include about 0.5 mg to 10 mg, preferably about 0.6 mg to 5 mg, and more preferably 0.7 mg to 3 mg.

The magnesium component may be any magnesium compound or pharmaceutically acceptable salt thereof, but more preferably is magnesium ascorbate or magnesium ascorbic acid, wherein the magnesium is typically present in about 5 to 20 weight percent of the complex. When complexed with vitamin C, this vitamin C source may be included in the overall percentage of vitamin C in the pharmaceutical composition.

Carotenoids are powerful antioxidants, and they include beta-carotene, canthaxanthin, zeaxanthin, lycopen, lutein, crocetin, and capsanthin for example. Beta carotene is a carotenoid which is predominantly found in the skin. A carotenoid component, preferably beta carotene, is present in about 0.1 to 5 weight percent, preferably 0.2 to 4 weight percent, and more preferably 0.3 to 3 weight percent in the pharmaceutical composition.

Additionally, a source of selenium may also be optionally added to the pharmaceutical composition. A selenium compound or pharmaceutically acceptable salt thereof may be used. Preferably, the selenium compound is selenium complexed with an amino acid. Most preferably, the selenium compound is L-selenomethionine, wherein the selenium is present in 0.1 to 5 weight percent of the complex. Selenomethionine is present in about 0.01 to 3 weight percent, preferably 0.05 to 2 weight percent, and more preferably at 0.1 to 1 weight percent in the pharmaceutical composition.

The pharmaceutical composition more preferably includes at lest one herb from the group of yellow dock, bupleurum, poria cocos, gentian root, myrrh gum, hawthorn berry extract, rosemary extract, wild yam root, wild yam extract, and marshmallow root.

Yellow Dock, *Rumex crispus*, is often used to treat skin disease, especially those involving some form of inflammation. The active constituents of yellow dock are rumicin and chrysarobin. Yellow Dock extract is typically present in the pharmaceutical composition in about 1 to 30 weight percent, preferably 3 to 25 weight percent, more preferably 5 to 20 weight percent.

Bupleurum, *Bupleurum falactum*, is known for its effect on the liver. The active constituents in bulpleurum are furfurol, sterol, and bupleurumol. The bupleurum is present in the present pharmaceutical composition at about 1 to 20 weight percent weight, preferably about 2 to 15 weight percent, and more preferably 3 to 10 weight percent.

The active constituents in poria cocos, *Lycoperdon solidum*, are tetracyclic titerpenic acids, polysaccharides, ergostol, choline, lipase, and protease. This herb is useful for eliminating excess fluids from the body. It is typically present in the pharmaceutical composition in about 1 to 20 weight percent, preferably about 2 to 15 weight percent, more preferably about 3 to 10 weight percent.

The bitter glycosides in gentian root, *Gentian lutea*, account for its use as a digestive bitter and liver disorder treatment. Gentian root is typically present in the pharmaceutical compositions at about 1 to 20 weight percent, preferably about 2 to 15 weight percent, more preferably about 3 to 10 weight percent.

Myrrh, *Commiphora myrrha*, has several oils, resins and gums that increase circulation and heart rate. Myrrh gum is used in the present pharmaceutical composition in about 1 to 20 weight percent, preferably about 2 to 15 weight percent, more preferably about 3 to 10 weight percent.

Hawthorn berry, *Crataegus supplement.*, can optionally be added to the pharmaceutical composition as well. This herb is useful in the treatment of heart disease. Crategolic acid, citric acid, tartaric acid, glavone, glycosides, and vitamin C are the active constituents of hawthorne berries. The hawthorn berry is typically present in about 0.5 to 8 weight percent, preferably about 0.6 to 6 weight percent, and more preferably 0.7 to 4 weight percent of the composition.

Rosemary contains aromatic oils that assist with stomach disorders, and salicylic acid. It is typically present in the pharmaceutical composition at about 0.5 to 8 weight percent, preferably about 0.6 to 6 weight percent, and more preferably about 0.7 to 4 weight percent of the composition.

Wild yam possesses glycoside saponins and diosgenins, hormonal precursors to cortical steroids that help reduce pain. It assists with problems of the liver and gall bladder, as well. It is present in the pharmaceutical composition at about 0.5 to 8 weight percent, preferably 0.6 to 6 weight percent, and more preferably about 0.7 to 4 weight percent.

The marshmallow root, *Althea officinalis*, acts as an anti-inflammatory. The mucilage in the herb soothes membranes thereby reducing inflammation. Marshmallow root is present in the pharmaceutical composition at about 0.5 to 8 weight percent, preferably about 0.6 to 6 weight percent, and more preferably about 0.7 to 4 weight percent of the composition.

The phrase "therapeutically effective amount" means the amount of the pharmaceutical composition that provides a therapeutic benefit in the protection, prevention, or treatment of skin damage resulting from exposure to UV light.

The magnitude of a prophylactic or therapeutic dose of the composition in the prevention or treatment of UV damage to skin will vary with the sensitivity of the person's skin and the route of administration. The dose, and perhaps

the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose range, for the conditions described herein, is from about 1 mg to about 2,000 mg administered in about one to ten doses orally. The preferred oral unit daily dose range should be from about 1 mg to 2,000 mg; more preferably about 400 mg to 1,600 mg; most preferably about 800 mg to 1,200 mg.

It is further recommended that children, patients aged over 65 years, and those with impaired renal or hepatic function initially receive low doses, and that they then be titrated based on individual response(s) or blood level(s). It may be necessary to use dosages outside these ranges in some cases, as will be apparent to those of ordinary skill in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient's response.

Although any suitable route of administration may be employed for providing the patient with an effective dosage of the composition according to the methods of the present invention, oral administration is preferred. Suitable routes include, for example, oral, rectal, arenteral, intravenous, topical, transdermal, subcutaneous, intramuscular, and similar forms of administration may also be employed. Suitable dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, suppositories, and the like, although oral dosage forms are preferred.

The pharmaceutical compositions used in the methods of the present invention include the active ingredients described above, and may also contain pharmaceutically acceptable carriers, excipients and the like, and optionally, other therapeutic ingredients. The compositions herein may also be administered in conjunction with, i.e., concurrently or sequentially, with other skin-protective pharmaceutical composition or other devices, such as a hat, umbrella and the like.

The term "pharmaceutically acceptable salt" refers to a salt prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic or organic acids. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, sulfuric, and phosphoric. Appropriate organic acids may be selected, for example, from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenoic, benzenesulfonic, stearic, sulfanilic, algenic, and galacturonic. Examples of such inorganic bases, for potential salt formation with the sulfate or phosphate compounds of the invention, include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc. Appropriate organic bases may be selected, for example from N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucamine), and procaine.

The compositions for use in the methods of the present invention include compositions such as suspensions, solutions and elixirs; aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like, in the case of oral solid preparations (such as powders, capsules, and tablets), with the oral solid preparations being preferred over the oral liquid preparations. The most preferred oral solid preparations are tablets and capsules.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compound for use in the methods of the present invention may also be administered by controlled release means and/or delivery devices such as those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions for use in the methods of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, or aerosol sprays, each containing a predetermined amount of the active ingredient, as a powder or granules, as creams, pastes, gels, or ointments, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the carrier with the active ingredient which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compressing or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet, cachet or capsule contains from about 1 mg to 2,000 mg of the active ingredient.

EXAMPLES

The invention is further defined by reference to the following examples describing in detail the preparation of the compound and the compositions used in the methods of the present invention, as well as their utility. The examples are representative, and they should not be construed to limit the scope of the invention.

Example 1: Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with the desired amount of powdered active ingredient as described above, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Example 2: Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, lecithin, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing the desired amount of the active ingredient. The capsules are washed and dried for packaging.

Example 3: Tablets

A large number of tablets were prepared by conventional procedures so that the dosage unit included: the desired amount of active ingredient as described herein, 6 milligrams of stearic acid, 7 milligrams of sorbitol, 1.1 milligrams of magnesium stearate, and 1 milligram of syloid.

Appropriate coatings may be applied to increase palatability or delay absorption. A specific therapeutic formulation of the pharmaceutical composition described herein is set forth in the table below:

INGREDIENTS	MG PER TABLET	PERCENT BY WEIGHT	CHEMICAL OR SCIENTIFIC NAME
Vitamin C 100%	200.00	18.5%	Ascorbic acid
Vitamin E Succinate	127.00	11.7%	D-alpha tocopheryl acid succinate
Yellow Dock Root	96.00	8.9%	*Rumex cripus*
Bupleurum	48.00	4.4%	*Bupleuri spp.*
Poria Cocos	48.00	4.4%	*Poria cocos*
Echinacea	48.00	4.4%	*Echinacea pallida*
Gentian Root	48.00	4.4%	*Gentiana spp.*
Golden Seal	48.00	4.4%	*Hydrastis canaderus*
Myrrh Gum	48.00	4.4%	*Commiphora molmol*
Echinacea (extract 1.5:1)	48.00	4.4%	*Echinacea angustifolium*
Quercetin Powder	40.00	3.7%	Quercetin dihydrate
Milk Thistle extract (83% silymarin)	40.00	3.7%	*Silybum marianum*
N-Acetyl Cysteine	40.00	3.7%	N-acetyl cysteine
Opti-Zinc® monomethionine (20%)	30.00	2.8%	Zinc monomethionine
Magnesium Ascorbate (20%)	30.00	2.8%	Magnesium ascorbate
Hawthorne Berry (extract 1:4)	20.00	1.9%	*Crataegus spp.*
Rosemary (extract 5:1)	20.00	1.9%	*Rosmarinus officinalis*
Wild Yam Root	19.00	1.8%	*Dioscorea villosa*
Manganese Ascorbate (6.00%)	17.00	1.5%	Manganese ascorbate
Wild Yam (extract 1-4)	14.00	1.3%	*Dioscorea villosa*
Marshmallow Root	14.00	1.3%	*Althea officinalis*
Beta Carotene (yields 1,250 iu per tablet)	8.00	0.7%	Beta carotene
Grape Seed Extract	5.00	0.5%	Proanthocyanidinis
Selenomethionine (0.50%)	4.00	0.4%	L-selenomethionine
Vitamin A Palmitate (yields 1,250 iu per tablet)	4.00	0.4%	Vitamin A palmitate
Copper Sebacate (14.00%)	1.10	0.1%	Copper Sebacate
Ginkgo Biloba Extract 50:1	1.00	0.1%	Ginkgo biloba

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These tablets are an example of a preferred embodiment of a unit dose according to the present invention.

Examples 4–6: Effectiveness of Skin-protectiveness Composition Against UV-Damage

Three separate tests were conducted to evaluate the potential of the present invention to change the photobiological responsiveness of the skin in human subjects. Each of the tests first evaluated the SPF of a sunscreen prior to using the present invention, and then evaluated the SPF of the sunscreen in conjunction with the present invention. The three sunscreens used in the tests were MURASUN® Hand, Neck, and Decollete Sunscreen, MURASUN® Daily Sunscreen, and MURASUN® Daily Sunblock available from Murad, Inc., El Segundo, Calif. Also, the formulation used in example 3 was used for the vitamin supplements administered.

In each of the tests, ten volunteers between the ages of 18 and 60 were selected having fair skin of types I–III, determined by the following guidelines:

a) 18 to 60 years of age;

b) Fair skinned with skintypes I–III, where:

I always burns easily; never tans (sensitive)

II always burns easily; tans minimally (sensitive)

III burns moderately; tans gradually (normal)

IV burns minimally; always tans well (normal)

V rarely burns; tans profusely (insensitive)

VI never burns; deeply pigmented (insensitive)

These panelists were first subjected to a determination of the pre-antioxidant vitamin supplement static sun protection factor (SPF) values. A sufficient number of 5×10 cm test site areas were outlined with a surgical marking pen on each subject's back between the scapulae and the beltline, lateral to the midline. These areas were designated for the Test Material and Standard, with an adjacent site designated for a concurrent Minimal Erythemal Dose (MED).

The MED is defined as the time interval or dosage of UV light irradiation sufficient to produce a minimal, perceptible erythema on designated test sites. Prior to the testing phase, the MED of the unprotected skin of each subject was determined by a progressive sequence of timed UV light exposures, graduated incrementally by 25 percent over the previous exposure. Sixteen to twenty-four hours after irradiation, the sites were evaluated for erythema according to the following scoring system:

0=Negative, no visible reaction

±=Minimal erythema

1+=Defined erythema

2+=Moderate erythema

3+=Severe erythema

A 0.1 ml or 0.1 g portion of the Test Material and of the Standard was applied to the appropriate designated test site and spread evenly over the site using a finger cot. After product application, each test area was subdivided into sites which were used for defined serial UV light exposure. A Xenon Arc Solar Simulator, commercially available from the Solar Light Company, Philadelphia, Pa., was used as the source of ultraviolet light. A continuous emission spectrum in the UV-B range (290–320 nanometers) was produced during the testing procedure by this instrument. Irradiation of the sites was begun no less than 15 minutes and no longer than 30 minutes after application.

Exposure times were selected for each site in treated areas based upon the previously determined MED of the unprotected skin and the expected SPF of the test material or the standard.

All test sites were evaluated 16 to 24 hours after irradiation to determine the minimal erythemal response.

Next a determination of the post-antioxidant vitamin supplement SPF values was made using the vitamin supplement formulation provided in Example 3.

Each of the volunteers was provided with the vitamin supplement tablets of the present invention with instructions to take the tablets twice daily.

The sites were outlined on the subject's back and the sunscreen application, waiting period and irradiation procedure, previously described, was followed. All test sites were evaluated 16 to 24 hours after irradiation to determine minimal erythemal responses.

The SPF for the Test Material and Standard for each subject was calculated according to the formula:

SPF=MED Test Material or Standard/MED Unprotected Control

The test results and conclusions for the three tests are presented below.

Example 4: MURASUN® Hand, Neck and Decollete Sunscreen

Example 4 was performed using MURASUN® Hand, Neck and Decollete Sunscreen. The MURASUN® Hand, Neck and Decollete Sunscreen has the following formulation:

MURAD

FORMULA FOR HAND, NECK & DECOLLETE HYDRATING CREAM SPF-15

Percentage Formula

Name Of Ingredient	% By Weight
1. Water (Aqua)	58.46%
2. Octyl Methoxycinnamnte	7.5
3. Glycolic Acid	5.6
4. Glycerin	5.00
5. Oxybenzone	4.00
6. Butylene Glycol	4.00
7. Sodium Hydroxide	2.00
8. DEA-Cetyl Phosphate	1.80
9. Glyceryl Stearate	1.5
10. PEG-100 Stearate	1.50
11. Magnesium Aluminum Silicate	1.30
12. Cetearyl Alcohol	1.00
13. Ceteareth-20	1.00
14. Dimethicone	1.00
15. Calcium Sodium Borosilicate	1.00
16. Keratin Amino Acids	0.10
17. C_{12-13} Alkyl Lactate	0.50
18. Lecithin	0.01
19. Tocopherol	0.01
20. Magnesium Ascorbyl Phosphate	0.01
21. Retinyl Palmitate	0.01
22. Corn (Zea Mays) Oil	0.01
23. Lemon (Citrus Medica Limonum) Peel Extract	0.10
24. Propylene Glycol	0.40
25. Sodium PCA	0.50
26. Panthenol	0.40
27. allantoin	0.10
28. Xanthan Gum	0.50
29. Disodium EDTA	0.10
30. Diazolidinyl Urea	0.30
31. Methylparaben	0.15
32. Butylparaben	0.06
33. Ethylparaben	0.05
34. Propylparaben	0.03
	100.00%

The SPF calculations obtained for each panelist regarding MURASUN® Hand, Neck and Decollete Sunscreen alone and MURASUN® Hand, Neck and Decollete Sunscreen with the present invention are represented in table 1. No adverse dermal irritations were observed on the treated area of any panelist.

Under the conditions of this study, the pre-antioxidant vitamin supplement (static) average Sun Protection Factor of MURASUN® Hand, Neck and Decollete Sunscreen was calculated to be 15.7.

Following the oral treatment, the post-antioxidant vitamin supplement Sun Protection Factor was calculated to be 16.1.

The test concluded that there was a 2.5% increase in the mean SPF value of the test sunscreen product following one week of twice daily ingestion of an antioxidant vitamin supplement.

TABLE 1

SPF Results for MURASUN® Hand, Neck and Decollete Sunscreen Used Alone and With Vitamin Supplement

Subject	Skin Type	Murasun® Hand, Neck and Decollete Pre-Antioxidant Vitamin Supplement	Murasun® Hand, Neck and Decollete Post-Antioxidant Vitamin Supplement
1)	II	15.0	18.7
2)	II	15.0	18.7
3)	II	15.0	15.0
4)	II	15.0	15.0
5)	II	15.0	15.0
6)	II	15.0	15.0
7)	II	18.7	18.7
8)	II	18.7	15.0
9)	II	15.0	15.0
10)	II	15.0	15.0
		15.7	16.1

Example 5: MURASUN® Daily Sunscreen

Example 5 was performed using MURASUN® Daily Sunscreen. The MURASUN® Daily Sunscreen has the following formulation:

MURAD

FORMULA FOR MURASUM DAILY SUNSCREEN SPF-15

Percentage Formula

Name of Ingredient	% by Weight
1. Water (Aqua)	61.27%
2. Octyl Methoxycinnamate	7.5
3. Dicaprylyl Maleate	5.00
4. Octyl Salicylate	5.00
5. Oxybenzone	4.00
6. Glycerin	5.00
7. Stearic Acid	3.00
8. PVP/Eicosene Copolymer	3.00
9. DEA-Cetyl Phosphate	2.00
10. Cetyl Alcohol	1.00
11. Dimethicone	0.20
12. Lecithin	0.01
13. Tocopherol	0.01
14. Magnesium Ascorbyl Phosphate	0.01
15. Lemon (Citrus Medica Limonum) Peel Extract	0.10
16. Propylene Glycol	0.40
17. Melanin	0.01
18. Glycolipids	0.10
19. Hyaluronic Acid	0.10
20. Sodium PCA	0.50

-continued

Name of Ingredient	% by Weight
21. Carbomer	0.23
22. Triethanolamine	0.41
23. Disodium EDTA	0.05
24. Diazolidinyl Urea	0.30
25. Methylparaben	0.20
26. Propylparaben	0.10
27. Titanium Dioxide	0.50
	100.00%

The SPF calculations obtained for each panelist regarding the SPF of MURASUN® Daily Sunscreen alone and MURASUN® Daily Sunscreen with the present invention are represented in Table 2. No adverse dermal irritations were observed on the treated area of any panelist.

Under the conditions of this study, the pre-antioxidant vitamin supplement (static) average Sun Protection Factor of Murasun® Daily Sunscreen was calculated to be 17.98.

Following the oral treatment, the post-antioxidant vitamin supplement Sun Protection Faetor was calculated to be 19.84.

The test concluded that there was a 10.34% inercase in the mean SPF value of the test sunscreen product following one week of twice daily ingestions of an antioxidant vitamin supplement.

TABLE 2

SPF Results for MURASUN ® Daily Sunscreen Used Alone and With Vitamin Supplement

Subject	Skin Type	Murasun ® Daily Sunscreen Pre-Antioxidant Vitamin Supplement	Murasun ® Daily Sunscreen Post-Antioxidant Vitamin Supplement
1)	II	15.0	18.7
2)	II	18.7	23.4
3)	II	18.7	18.7
4)	II	18.8	23.4
5)	II	18.7	18.7
6)	II	18.7	23.4
7)	II	18.7	18.7
8)	II	15.0	15.0
9)	II	18.7	23.4
10)	II	18.8	15.0
		17.98	19.84

Example 6: MURASUN® Daily Sunblock

Example 6 was performed using MURASUN® Daily Sunblock. The MURASUN® Daily Sunblock has the following formulation:

MURAD

FORMULA FOR MURASUN DAILY SUNBLOCK SPF-15

Percentage Formula

Name of Ingredient	% by Weight
1. Water (Aqua)	68.55%
2. Propylene Glycol Dicaprylate/Dicaprate	10.00
3. Butylene Glycol	6.00
4. Titanium Dioxide	5.60

-continued

Name of Ingredient	% by Weight
5. Isodecyl Neopentanoate	3.00
6. Cetyl Alcohol	2.00
7. Glyceryl Stearate	1.25
8. PEG-100 Stearate	1.25
9. Potassium Cetyl Phosphate	0.10
10. Lecithin	0.01
11. Tocopherol	0.01
12. Magnesium Ascorbyl Phosphate	0.01
13. Sodium PCA	0.10
14. Polyisoprene	0.03
15. Soybean (Glycine Soja) Sterol	0.02
16. Retinyl Palmitate	0.01
17. Ascorbyl Palmitate	0.01
18. Lemon (Citrus Medica Limonum) Peel Extract	0.10
19. Propylene Glycol	0.40
20. Xanthan Gum	0.25
21. Carbomer	0.25
22. Triethanolamine	0.30
23. Disodium EDTA	0.10
24. Diazolidinyl Urea	0.30
25. Methylparaben	0.25
26. Propylparaben	0.10
	100.00%

The SPF calculations obtained for each panelist regarding the SPF of MURASUN® Daily Sunblock alone and with the vitamin supplement are represented in Table 3. No adverse dermal irritations were observed on the treated area of any panelist.

Under the conditions of this study, the pre-antioxidant vitamin supplement (statie) average Sun Protection Factor of Murasun® Daily Sunblock was calculated to be 17.24.

Following the oral treatment, the post-antioxidant vitamin supplement Sun Protection Factor was calculated to be 18.63.

This test concluded that there was a 7.9% increase in the mean SPF value of the test sunscreen product following one week of twice daily ingestion of an antioxidant vitamin supplement.

TABLE 3

SPF Results for MURASUN ® Daily Sunblock Used Alone and With Vitamin Supplement

Subject	Skin Type	Murasun ® Daily Sunblock Pre-Antioxidant Vitamin Supplement	Murasun ® Daily Sunblock Post-Antioxidant Vitamin Supplement
1)	II	18.7	18.7
2)	II	18.7	18.7
3)	II	15.0	23.4
4)	II	18.8	23.4
5)	II	18.7	18.7
6)	II	15.0	15.0
7)	II	18.7	15.0
8)	II	15.0	15.0
9)	II	15.0	23.4
10)	II	18.8	15.0
		17.24	18.63

Although preferred embodiments of the invention have been described in the foregoing Detailed Description of the Invention, it will be understood that the invention is not limited to the embodiments disclosed but is capable of numerous modifications without departing from the spirit and scope of the present invention. It will be understood that

the chemical details may he slightly different or modified by one of ordinary skill in the art without departing from the methods and compositions disclosed and taught hy the present invention.

What is claimed is:

1. A pharmaceutical composition for the protection from or treatment of skin damage resulting from exposure to skin damaging light in a patient comprising:

at least one primary antioxidant component in an amount sufficient to reduce free radicals in the patient's hody;

at least one anti-inflammatory component in an amount sufficient to reduce inflammation of the patient's skin; and

at least one immunity boosting component in an amount sufficient to stimulate the patient's immune system response to protect skin or facilitate repair of damaged skin.

2. The pharmaceutical composition of claim 1, wherein the primary antioxidant componcnt is present in ahout 5 to 50 weight percent, the anti-inflammatory component is present in about 5 to 40 weight percent, and the immunity hoosting component is prescnt in ahout 1 to 20 weight percent of the composition.

3. The pharmaceutical composition of claim 1, wherein the primary antioxidant component comprises at least one of a catechin-hased preparation, a vitamin A source, a ginko biloba extract, a silymarin source, a quercetin compound, or a vitamin C source.

4. The pharmaceutical composition of claim 3, wherein the catechin-based preparation is a proanthanol or proanthocyanidin, the vitamin A source is vitamin A palmitate, the silymarin source is milk thistle extract, the quercitin compound is quercitin dihydrate, and the vitamin C source is an ascorhic acid compound, or a salt or ester thereof.

5. The pharmaceutical composition of claim 4, wherein the primary antioxidant component comprises proanthocyanidin prcsent in about 0.1 to 5 weight percent, vitamin A palmitate present in about 0.1 to 5 weight percent, ginkgo biloba extract present in ahout 0.01 to 3 weight percent, the quercetin dihydrate and is present in ahout 1 to 20 weight percent, ascorbic acid present in about 5 to 50 weight percent, and milk thistle extract present in ahout 1 to 20 weight percent.

6. The pharmaceutical composition of claim 1, wherein the anti-inflammatory component comprises a vitamin E source, a zinc compound or a pharmaceutically acceptable salt thereof.

7. The pharmaceutical composition of claim 6, wherein the vitamin E source is a sulfate or succinate complex of vitamin E and the zinc compound is a complex of zinc and an amino acid.

8. The pharmaceutical composition of claim 7, wherein the vitamin E source is D-alpha tocophcrol acid succinatc present in about 5 to 40 weight percent, and the zinc compound is zinc monomethinone present in about 1 to 12 wcight percent, whcrein the zinc is prefcrably present in about 10 to 30 weight percent of the complex.

9. The pharmaceutical composition of claim 1, wherein the immunity boosting component comprises at least one of echinacea, an echinachea extract, or golden seal.

10. The pharmaceutical composition of claim 1, wherein the composition further comprises a pharmaceutically acceptahle carrier or excipient.

11. The pharmaceutical composition of claim 1, further comprising one or more of a cysteine component, a magnesium component, manganese component, a copper component, a selenium component, or a carotenoid component.

12. The pharmaceutical composition of claim 11, wherein the cysteine component is N-acetyl cysteine and is present in about 1 to 10 weight percent, the magnesium component is magnesium ascorbate and is present in ahout 1 to 10 weight percent, wherein the magnesium is present in about 10 to 30 weight percent of the complex, the manganese component is manganese ascorhate and is present in ahout 0.5 to 10 weight percent, wherein manganese is present in ahout 5 to 20 weight percent of the complex, the copper component is copper sehacate and is present in ahout 0.01 to 5 weight percent, wherein the copper is present in ahout 5 to 20 weight percent of the complex, and the carotenoid component is heta carotene and is present in ahout 0.1 to 5 weight percent.

13. The pharmaceutical composition of claim 11, further comprising at least onc of the wild yam root, wild yam extract, yellow dock, bupleurum, poria cocos, gentian root, myrrh gum, hawthorn herry extract, or rosemary extract.

14. The pharmaceutical composition of claim 13, wherein the amount of wild yam root, wild yam extract, marshmallow root, hawthorn berry extract, and rosemary extract, when present, is about 0.5 to 8 weight percent each, the amount of yellow dock, when present, is about 1 to 30 weight percent, and the amount of buplcurum, poria cocos, gentian root and myrrh, when present, is ahout 1 to 20 weight percent each.

15. A method for treating and protecting skin from damage caused by the exposure to sunlight, which comprises administering the pharmaceutical composition of claim 1 in therapeutically effective to increase the sun protection factor of the skin.

16. Thc method of claim 15, wherein the composition is administered orally.

17. The method of claim 16, wherein the composition is administered as a tablet or capsule having ahout 1 mg to 2,000 mg of composition.

18. The method of claim 17, wherein the tahlet or capsule has about 400 mg to 1,600 mg of composition.

19. The method of claim 18, wherein the tahlet or capsule has ahout 800 mg to 1,200 mg of composition.

20. The method of claim 15, which further comprises concurrently or suhsequently administering at least one additional pharmaceutical composition comprising a sunscreen, a nutritional supplement or a topical application used to treat or protcct the skin from damage from the exposure to skin damaging light.

21. The method of claim 20, wherein the additional pharmaceutical composition comprises:

a sunscreen having at least one of the following active ingredients: titanium dioxide, zinc oxide, talc, red veterinary petrolatum, octyl methoxycinnamate, oxyhenzone, octyl salicylate, or para-aminobenzoic acid;

a nutritional supplement having at least one of the following: antioxidants, vitamin E, vitamin C, or carotenoids; or

a topical application having at least one of the following: vitamin A, vitamin E, vitamin C, or alpha-hydroxy acids.

* * * * *